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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

RECOMBINANT DNA ADVISORY COMMITTEE

MINUTES OF MEETING[1]

JUNE 1, 1984

The Recombinant DNA Advisory Committee (RAC) was convened for its thirtieth meeting at 9:00 a.m. on June 1, 1984, in Building 31, Conference Room 6, National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland 20205. Mr. Robert Mitchell (Chair), Attorney at Law in California, presided. In accordance with Public Law 92-463, the meeting was open to the public from 9:00 a.m. to 3:30 p.m. The meeting was closed to the public from 3:30 p.m. to 5:25 p.m. for review of proposals involving proprietary information. The following were present for all or part of the meeting:

Committee members:

Barbara Bowman	Wolfgang Joklik	Fred Rapp
Royston Clowes	Arthur Landy	Mark Saginor
L. Albert Daloz	Myron Levine	John Scandalios
Nina Fedoroff	Gerard McGarrity	Frances Sharples
David Friedman	John McGonigle	LeRoy Walters
Susan Gottesman	Robert McKinney	Pieter Wensink
John Harvin	Robert Mitchell	Anne Witherby
King Holmes	Thomas Pirone	William J. Gartland, Jr. (Executive Secretary)

A committee roster is attached (Attachment I).

Ad hoc consultants:

George Lacy, Virginia Polytechnic Institute State University
David Pimentel, Cornell University
Anne Vidaver, University of Nebraska

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[1]The RAC is advisory to the NIH, and its recommendations should not be considered as final or accepted. NIH action on two of these recommendations was published in the Federal Register on September 13, 1984 (49 FR 36052). The Office of Recombinant DNA Activities should be consulted for NIH policy on specific issues.

Non-voting members:

William Beisel, Department of Defense
Howard Berman, Veterans Administration
John Cox, Department of Commerce
Jack Fowle, Environmental Protection Agency
Morris Levin, Environmental Protection Agency
Herman Lewis, National Science Foundation
Henry Miller, Food and Drug Administration
Sue Tolin, Department of Agriculture
William Walsh, Department of State

National Institutes of Health staff:

Stanley Barban, NIAID
Manuel Barbeito, OD
Emmett Barkley, OD
Becky Connors, NIAID
Irving Delappe, NIAID
Thomas Flavin, NIAID
Leslie Fink, NICHD
Susan Gerhold, OD
Rosalind Gray, OD
Bowen Hosford, OD
John Irwin, OD
Rachel Levinson, OD
Elizabeth Milewski, NIAID
Stanley Nagle, NIAID
Don Ralbovsky, OD
Bernard Talbot, NIAID

Other

Stanley Abramson, Environmental Protection Agency
Joan Alper, Biometric Research Institute
Bonnie Ashbaugh, Industrial Biotechnology Association
Yvonne Baskin, Science Writer
Ralph Benzinger, National Science Foundation
Fred Betz, Environmental Protection Agency
Robert Birnk, Environment Protection Agency
Irene Brandt, Eli Lilly and Company
Winston Brill, Cetus Madison Corporation
Bradley Brockbank, ICF, Inc.
Steve Budiansky, Nature Magazine
Patricia Campbell, Uniformed Services University of the Health Sciences
Margaret Champion, Genetics Institute
Chia Chen, OSHA, Department of Labor
Jeff Christy, Blue Sheet, FDC Reports, Inc.
Michael Cross, New Scientist Magazine
Mary Ellen Curtin

Ellen Daniell, University of California, Berkeley
Charles Eby, Monsanto Company
Gershon Fishbein, Environews, Inc.
John Galet, Schering-Plough Corporation
David Gelfand, Cetus Corporation
Harvey Giss, Litton Bionetics
David Glass, BioTechnica International, Inc.
Alan Goldhammer, Industrial Biotechnology Association
Dan Greenberg, Science and Government Report
Carol Gronbeck, Genentech, Inc.
Marlin Harmon, Tech S Corporation
Zsolt Harsanyi, E. F. Hutton
Judy Hautala, Genex Corporation
Kathleen Henderson, Miles Laboratories, Inc.
Philip Hilts, Washington Post
Ann Hollander, Environmental Protection Agency
Randall Holmes, Uniformed Services University of the Health Sciences
Marian Hunt, Hunt Reporting Company
Evelyn Hurlburt, Johns Hopkins University
Nicholas Seay, Isaksen, Lathrop, Esch, Hart, and Clark
Dorothy Jessop, Department of Agriculture
Irving Johnson, Eli Lilly and Company
Judy Johnson, Library of Congress
Larry Johnson, AMGen
Mary Jane Johnson, Pall Corporation
Roger Johnson
Chris Joyce, New Scientist Magazine
Alan Kaplan, Attorney
Geoffrey Karny, Finnegan, Henderson, Farabow, Garrett, and Dunner
John Keene, Abbott Laboratories
Lorraine Kershner, Office of Assistant Secretary for Health, HHS
Rihito Kimura, Kennedy Institute
E. L. Korwek, Keller and Heckman Law Offices
Margaret Kriz, Bureau of National Affairs, Inc.
Steve Lawton, Pierson, Ball, and Dowd
Jane MaGee, Agrigenetics
Kenneth Martinez, National Institute for Occupational Safety and Health
Carl Mazza, Environmental Protection Agency
Mary Ellen McCarthy, McGraw-Hill Publications Company
James McCullough, Library of Congress
Kim McDonald, Chronicle of Higher Education
Marylin McDonald, Foundation on Economic Trends
Gerald Mercer, Miles Laboratories, Inc.
Jeffrey Meyer, Cleary, Gottlieb, Steen, and Hamilton
Julie Miller, Science News
Bernie Mlynczak, Monsanto Company
William Muth, Eli Lilly and Company
Robert Nicholas, Committee on Science and Technology, U.S. House of Representatives
Gary Noble, Centers for Disease Control

Colin Norman, Science Magazine
Jerry Norman, Gist-Brocades Fermentation Industries
Alison O'Brien, Uniformed Services University of the Health Sciences
Vinson Oviatt, World Health Organization
C. W. Pettinga, Eli Lilly and Company
Stephen Pijar, Food and Drug Administration
Tabitha Powledge, Biotechnology Magazine
Harvey Price, Industrial Biotechnology Association
Jeremy Rifkin, Foundation on Economic Trends
Monica Riley, American Society for Microbiology
Jane Rissler, Environmental Protection Agency
Marvin Rogul, The Rogul Group
Harold Schmeck, New York Times
Mark Segal, Environmental Protection Agency
James Seligman, Centers for Disease Control
Janet Shoemaker, American Society for Microbiology
Arthur Stern, Environmental Protection Agency
Trevor Suslow, Advanced Genetic Sciences, Inc.
Laura Tangley, Bioscience
Jeff Trewhitt, McGraw-Hill World News
Lidia Watrud, Monsanto Company
James Wu, Hoffmann-LaRoche, Inc.

I. CALL TO ORDER AND OPENING REMARKS

Mr. Mitchell, Chair, called the meeting of the Recombinant DNA Advisory Committee (RAC) to order. Mr. Mitchell said the RAC had been convened in accordance with the April 24, 1984, Federal Register (49 FR 17672) announcement to review those items described in that announcement. Dr. Gartland informed Mr. Mitchell that a quorum was present.

Mr. Mitchell welcomed six new committee members: Dr. Barbara Bowman of the University of Texas; Dr. Thomas Pirone of the University of Kentucky; Dr. Fred Rapp of the University of Pennsylvania; Dr. Frances Sharples of Oak Ridge National Laboratory; Dr. LeRoy Walters of Georgetown University; and Mrs. Ann Witherby of Boston, Massachusetts.

Mr. Mitchell also welcomed three ad hoc consultants to the RAC: Dr. George Lacy of Virginia Polytechnic Institute; Dr. David Pimentel of Cornell University; and Dr. Anne Vidaver of the University of Nebraska.

Mr. Mitchell said in order to move expeditiously on a full agenda he would recognize individuals in the following order: primary reviewers; other RAC members; ad hoc consultants to RAC; non-voting representatives to RAC; RAC's administrative staff; members of the public who submitted written documents or comments; and finally other members of the public who wish to comment. Mr. Mitchell suggested members of the public indicate their wish to be recognized to staff to facilitate the process.

II. MINUTES OF THE FEBRUARY 6, 1984, MEETING

Mr. Daloz said he found the minutes (tab 1166) of the February 6, 1984, RAC meeting to be in order and moved approval. He also congratulated Mr. Mitchell, Dr. Gartland, and Dr. Talbot for having conducted a very clear meeting. Dr. Harvin concurred and seconded the motion.

Dr. McKinney moved that tab 1147, a letter from Drs. David Pramer and Harlyn O. Halvorson of the American Society for Microbiology (ASM) dealing with the paper by Drs. Giles and Whitehead [see V. Discussion of Letter from Congressman Gore Including Paper on Reassociation of a Modified Mycorrhiza with the Host Plant Roots in the minutes of the February 6, 1984, meeting of the RAC] be appended to the minutes of the February 6, 1984, RAC meeting. Dr. McKinney felt this letter clarified the major issues and supported the conclusions drawn by Dr. Fedoroff in her February 6 review of the Giles and Whitehead paper. Dr. Fedoroff seconded the motion. By a show of hands the RAC, with no opposed votes, voted to append tab 1147 to the minutes of the February 6, 1984, meeting.

Dr. Fedoroff requested that her name, which had been inadvertently omitted, be added to the list of RAC members attending the February 6 meeting. Dr. Walters requested that a typographical error be corrected. Mr. Mitchell

called for the vote on the motion to approve the minutes of the February 6, 1984, RAC meeting as amended. By a vote of sixteen in favor, none opposed, and no abstentions, the motion carried.

III. AMENDMENT OF APPENDIX G - PHYSICAL CONTAINMENT

Dr. McKinney explained the history of the proposal (tab 1156/VI, 1171) to amend Appendix G, Physical Containment, of the Guidelines.

The booklet, Classification of Etiologic Agents on the Basis of Hazard (U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, Office of Biosafety, Atlanta, Georgia 30333), has served since 1969 as a general reference for laboratory activities utilizing infectious agents. The fourth edition of that booklet (July 1974) was incorporated in the 1978 revision of the National Institutes of Health (NIH) Guidelines for Research Involving Recombinant DNA Molecules and has since been a part of those Guidelines as Appendix B.

Now an Interagency Working Group constituted by the Centers for Disease Control (CDC) and the NIH has prepared a new set of guidelines for laboratory research with etiologic agents. These new guidelines are entitled Biosafety in Microbiological and Biomedical Laboratories. The CDC/NIH guidelines designate four categories of biosafety levels for laboratory operation: Biosafety Levels 1, 2, 3, and 4. These levels are comparable to the P1, P2, P3, and P4 containment levels described in the NIH Guidelines for Research Involving Recombinant DNA Molecules.

The CDC/NIH Interagency Working Group proposed that RAC consider recommending a revision of the description of the P levels in the NIH Guidelines so that these descriptions would correspond to the biosafety levels set forth in the document Biosafety in Microbiological and Biomedical Laboratories.

Dr. McKinney said the P-levels of physical containment described in the NIH Guidelines were the first clear definition of practices, procedures, and facility conditions promulgated for microbiological research. Dr. McKinney said the P-levels have served well; however, these designations have been extended into a number of areas where they are inappropriate. Dr. McKinney felt institution of a common language corresponding to the biosafety levels set forth in the document Biosafety in Microbiological and Biomedical Laboratories would aid in eliminating the resultant confusion from these areas. He anticipated that common language describing biosafety levels could be implemented in general microbiology laboratories, in recombinant DNA laboratories, and in laboratories dealing with oncogenic viruses.

Dr. McKinney said the language proposed in the April 24, 1984, Federal Register would not substantively change Appendix G of the Guidelines. Dr. Barkley of the NIH Division of Safety said Biosafety Level 2 (BL2) differs from P2 in six major ways: (1) BL2 specifically gives responsibility to the laboratory director for establishing a laboratory access policy; (2) BL2 recognizes the problem of skin contamination; (3) BL2 expands the

safeguards appropriate for the safe handling of needles and syringes; (4) BL2 requires a biosafety manual be established to govern actions within the laboratory; (5) BL2 emphasizes concentration and volume concerns; and (6) BL2 emphasizes the importance of hand washing by requiring a sink in a BL2 facility.

Dr. Barkley said the proposed Biosafety Level 3 (BL3) differs from P3 by three minor modifications: (1) BL3 requires a baseline serum sample from people who will work in the BL3 facility be collected and stored; (2) BL3 requires a biosafety manual for governing operations within the facility; and (3) BL3 requires the laboratory be equipped with self-closing doors.

Dr. McGarrity said the proposal is a very healthy development. He noted that some "housekeeping" modifications may be required should this proposal be accepted by the NIH; the proposed language recommending BL1 containment conditions for exempt experiments under Appendix C differs from the language of a proposed modification of Appendix C to be discussed later in the meeting. [See IV. Amendment of Procedures for Scale-Up of Organisms Listed in Appendix C of these minutes.]

Dr. McGarrity asked Dr. Barkley if the National Cancer Institute (NCI) was attempting to align language describing conditions for proper handling of oncogenic viruses with the language of the booklet Biosafety in Microbiological and Biomedical Laboratories. Dr. Barkley replied that an NCI committee is moving to adopt this language and the assessment philosophy which emphasizes inhalation hazards as the principal parameter for assigning BL3 containment. Dr. Barkley said it appears the oncogenic viruses will be placed in the BL2 category because of the absence of substantive evidence that any of the retroviruses represent an inhalation risk.

Dr. Landy pointed out that at present the NIH Guidelines have no containment listing assigned for use of oncogenic viruses. He questioned whether RAC should continue to leave the creation of such a listing to another agency or develop its own classification for oncogenic viruses.

Dr. McGarrity asked if the language of the proposed Appendix G revision had been taken in toto from the CDC/NIH booklet. Dr. Barkley replied that the descriptions in the CDC/NIH document apply specifically to organisms shown to cause disease in laboratory workers. In the proposed Appendix G language, the terms "infectious agents" or "etiologic agents" are replaced by the phrase "organisms that contain recombinant DNA molecules." This phrase is consistent with the emphasis of the NIH Guidelines for Research Involving Recombinant DNA Molecules.

Dr. McGarrity referred to the proposed specification in Appendix G-II-A-1-h for wearing laboratory coats, gowns, or uniforms "to prevent contamination or soiling of street clothes." He felt a laboratory safety manual should be more concerned with the prevention of contamination than with soiling of clothing.

Dr. McGarrity noted that Appendix G-II-B-3-a-(1) refers to "...harvesting infected tissues from animals or eggs..." while Appendix G-II-C-3-a refers to "...harvesting of tissues or fluids from experimental animals and embryonate eggs...." The word "infected" is not used in Appendix G-II-C-3-a even though Appendix G-II-B specifications refer to the BL2 level of containment while Appendix G-II-C specifications refer to the more stringent BL3 containment level. Dr. Barkley said both Appendix G-II-B-3-a-(1) and Appendix G-II-C-3-a should contain the word "infected."

Dr. McGarrity then referred to the language of Appendix G-II-D-2-(1) which requires that:

> "Laboratory animals involved in experiments requiring BL4 level physical containment shall be housed either in cages contained in Class III cabinets or in partial containment caging systems (such as Horsfall units [11]), open cages placed in ventilated enclosures, or solid-wall and -bottom cages placed on holding racks equipped with ultraviolet irradiation lamps and reflectors that are located in a specially designed area in which all personnel are required to wear one-piece positive pressure suits."

Dr. McGarrity said UV irradiation must be regularly monitored to be efficient and asked if Dr. McKinney could offer some rationale for the recommendation for UV irradiation. Dr. McKinney replied that Appendix G-II-D-2-(1) refers to a high containment BL4 facility where critical attention is paid to monitoring. He said a number of studies demonstrate the efficacy of UV lamps attached to animal racks for minimizing aerosol exposure within animal facilities.

Dr. Rapp regretted the departure from the P designations. He said it is easy for committees to change the Guidelines to the BL designations; but the P designations are now part of a tradition and will undoubtedly continue to be used. Dr. Barkley agreed that the P designations will probably be referenced for many years. He thought, however, that commonality of language and substance in laboratory biosafety designations is an important goal.

Dr. Rapp asked if "chewing" is considered to be "eating." He also asked if self-closing doors could be spring-loaded or if they had to be electrical. Dr. Barkley responded that "chewing" is defined as "eating;" the emphasis is on keeping things out of the mouth. Dr. Barkley said the requirement for self-closing doors may be met by spring-loaded devices.

Dr. McKinney referred the RAC to a letter from Mr. C. Searle Wadley and Dr. John H. Keene of Abbott Laboratories (tab 1171). Dr. McKinney said this letter expressed concern that some language in the Guidelines may be confusing and suggested language be added to Section III-D-4 to emphasize the need for appropriate containment for exempt experiments. The letter suggested exempt experiments "be performed at the appropriate biosafety level for the host or recombinant organism (for biosafety levels see Biosafety in Microbiological and Biomedical Laboratories)." Dr. McKinney

said there may be potential for confusion in the Guidelines because Appendix A and Appendix C both list organisms "exempt" from the Guidelines. To address this concern Dr. McKinney suggested the word "exemptions" in Appendix A be replaced with the word "exclusions." Mr. Mitchell suggested such a modification in the Guidelines as well as that proposed in tab 1171 would have to be published in the Federal Register for 30 days of public comment. Dr. McKinney agreed this issue would be better discussed at a future RAC meeting.

Dr. McKinney moved adoption of the proposal to amend Appendix G. Dr. McGarrity seconded the motion. By a vote of twenty in favor, none opposed, and no abstentions, the motion was carried.

IV. AMENDMENT OF PROCEDURES FOR SCALE-UP OF ORGANISMS LISTED IN APPENDIX C

Dr. McKinney introduced the proposal (tab 1156/I, 1154, 1163, 1173, 1174) to modify procedures for large-scale operations involving organisms listed in Appendix C. He said the proposed amendment has a lengthy and complicated history.

In May 1983, Dr. Irving S. Johnson of Eli Lilly and Company proposed that procedures be modified for experiments involving more than 10 liters of culture of "exempt" organisms listed in Appendix C of the NIH Guidelines for Research Involving Recombinant DNA Molecules. In September 1983, Dr. Max Marsh of Lilly Research Laboratories offered an alternate modification of Appendix C and requested it be referred to the RAC Large-Scale Review Working Group. The proposals were reviewed by the RAC at its September 19, 1983, meeting and referred to the Large-Scale Review Working Group. The Large-Scale Review Working Group met on February 7, 1984. After evaluating data and discussing the issues, the Large-Scale Review Working Group proposed the following modifications to the Guidelines:

(1) In Appendix K-II-D of Appendix K-II, P1-LS Level, the word "minimize" would be substituted for "prevent." Appendix K-II-D would read as follows:

> "Appendix K-II-D. Exhaust gases removed from a closed system or other primary containment shall be treated by filters which have efficiencies equivalent to HEPA filters or by other equivalent procedures (e.g., incineration) to minimize the release of viable organisms containing recombinant DNA molecules to the environment."

(2) The second paragraph of Appendix C-II, Experiments Involving E. coli K-12 Host-Vector Systems; Appendix C-III, Experiments Involving Saccharomyces cerevisiae Host-Vector Systems; and Appendix C-IV, Experiments Involving Bacillus subtilis Host-Vector Systems; would be modified to read as follows:

> "For these exempt laboratory experiments, P1 physical containment conditions are recommended."

(3) A paragraph would be added following the second paragraph of Appendix C-II, Appendix C-III, and Appendix C-IV. That paragraph would read as follows:

"For large-scale fermentation experiments P1-LS physical containment conditions are recommended. However, following review by the IBC of appropriate data for a particular host-vector system, some latitude in the application of P1-LS requirements as outlined in Appendix K-II-A through K-II-F is permitted."

(4) A reference to Appendix C would be added to the fourth sentence of Appendix K-I, Selection of Physical Containment Levels. That sentence would read as follows:

"The P1-LS level of physical containment is required for large-scale research or production of viable organisms containing recombinant DNA molecules which require P1 containment at the laboratory scale (See Appendix C)."

As a possible substitute, NIH staff proposed an alternate modification of Appendix K-I, Selection of Physical Containment Levels; the NIH staff alternative was published for comment in the April 24, 1984, Federal Register notice with the working group recommendations. In the NIH staff alternate modification the following sentence would be added following the fourth sentence of Appendix K-I, Selection of Physical Containment Levels:

"(The P1-LS level of physical containment is recommended for large-scale research or production of viable organisms for which P1 is recommended at the laboratory scale such as those described in Appendix C.)"

Dr. McKinney said the working group proposal offers some flexibility in application while requiring Institutional Biosafety Committee (IBC) oversight.

Dr. McGarrity concurred with Dr. McKinney's remarks. He said that while he had not supported Dr. Johnson's original proposal, he was comfortable with the language and intent of the working group proposal. He noted that although the guidelines on laboratory scale experiments have been revised several times, the large-scale procedures in Appendix K have experienced no major revisions.

Dr. Wensink said he preferred the alternative language offered by NIH staff to the working group language offered in item four. He suggested some other word be substituted for the word "experiments" in the third item of the working group proposal as these modifications refer not only to experiments but also to production procedures.

In addition, Dr. Wensink suggested the language of the third item of the proposal be modified as follows:

"For large-scale, e.g. greater than 10 liters of culture, fermentation of these host-vector systems, P1-LS physical containment conditions are recommended. These fermentations require prior IBC review and approval. Following review by the IBC of appropriate data for the particular host-vector system, the IBC may permit more latitude in the application of P1-LS requirements as outlined in Appendix K-II-A through K-II-F."

Dr. Wensink suggested he would offer a motion concerning these proposed alterations. Mr. Mitchell asked Dr. Wensink if he would wait until all comments on the proposal had been heard before offering a motion.

Dr. McKinney felt the word "experiments" could be applied to large-scale systems; he felt this word captured the intent of the Guidelines. Dr. Wensink said he was suggesting the word "fermentations" be substituted for "experiments" but he could appreciate Dr. McKinney's opinion.

Dr. Miller of the Food and Drug Administration (FDA) said FDA has a great deal of experience with the oversight of large-scale fermentations. He said FDA endorses the proposed amendments as they clarify the NIH Guidelines and are consistent with FDA's goal of establishing flexible standards.

Dr. McKinney said he would proceed by offering a separate motion on each proposed item of the working group proposal. He moved acceptance of item one of the proposal. Dr. Wensink seconded the motion.

By a vote of twenty in favor, none opposed, and no abstentions, the motion carried.

Dr. Wensink moved RAC accept the alternative NIH staff language of item four of the proposed amendment. Dr. McKinney seconded the motion.

By a vote of twenty in favor, none opposed, and no abstentions, the motion was carried.

Dr. Wensink said he would drop his suggestion to eliminate the word "experiment" in item three. Instead, he moved acceptance of items two and three with the proviso that the language of the fifth paragraph of Appendices C-II, C-III, and C-IV be moved to proposed item three. The language of Appendices C-II, C-III, and C-IV reads as follows:

"Large-scale experiments (e.g., more than 10 liters of culture) require prior IBC review and approval (See Section III-B-5)."

Dr. Talbot pointed out that the status of the requirement for IBC review of large-scale procedures would be unclear under Dr. Wensink's proposed modification since Dr. Wensink proposes to move this paragraph from the exceptions to exemptions section into the exemptions section. Dr. Talbot preferred the language proposed by the Large-Scale Review Working Group. Dr. Wensink agreed to drop his proposed modification. He moved acceptance

of the proposed language of items two and three as published in the April 24, 1984, Federal Register announcement. Dr. McKinney seconded the motion.

The RAC approved the motion to accept items two and three as published in the April 24, 1984, Federal Register by a vote of twenty-one in favor, none opposed, and no abstentions.

Dr. Landy said he wished to comment for the record; he felt IBC review and approval should not be required for large-scale experiments involving the organisms listed in Appendix C.

V. PROPOSED GUIDELINES FOR SUBMISSION UNDER APPENDIX L

Dr. McGarrity offered some background information on the proposed guidelines (tabs 1156/III, 1164, 1168) for submissions under Appendix L of the NIH Guidelines. Appendix L, Release into the Environment of Certain Plants, specifies conditions under which certain plants may be approved for release into the environment.

Dr. McGarrity said proposals involving release into the environment of plants not covered by Appendix L would be reviewed under Section III-A-2 of the NIH Guidelines. These proposals would be subject to review and approval by the IBC, the full RAC, and NIH.

Dr. McGarrity said RAC recognized the need for some standardized format for submission of "relevant information under Appendix L." The Plant Working Group, therefore, developed a draft guidance document for investigators submitting proposals under Appendix L. The draft document was submitted to the RAC for its consideration at the February 6, 1984, meeting and comments at that meeting suggested the document should specify additional information requirements. In response, the RAC Working Group on Release into the Environment met on April 9, 1984, to consider further information requirements for submission under Appendix L. The working group modified the draft document which was then published for public comment in the April 24, 1984, Federal Register (49 FR 17672). The document was again reviewed and modified by the Working Group on Release into the Environment at its May 31, 1984, meeting.

Dr. McGarrity said this modified document entitled Proposed Guidelines for Submissions under Appendix L (distributed at the RAC meeting) deals only with plants covered by Appendix L. The document does not address other plants or microorganisms. A similar document addressing field testing of microorganisms will be drafted in the future.

Dr. McGarrity said data requirements in the document are divided into three major informational areas: (1) a description of the plant materials; (2) information regarding the vector and the method of introduction into the plant; and (3) characteristics and monitoring of the plants in the greenhouse and growth chamber and under field conditions.

Dr. McGarrity said the guidance document represents a significant development in improving submission of information for experiments involving field testing of plants containing recombinant DNA. He said the guidance document specifies standard information requirements and at the same time can be modified as the technology develops and evolves. Dr. McGarrity said the proposals submitted in accordance with this guidance will undergo a case-by-case review as it would be very difficult if not impossible to devise a standard checklist containing every parameter involved in environmental release applications.

Dr. Clowes added that the document developed at the May 31, 1984, meeting of the Working Group on Release into the Environment does not differ substantively from the document which appeared in the April 24, 1984, Federal Register.

Dr. Gottesman said the guidance document should be a document which is modified as circumstances require; it should not be made part of the NIH Guidelines.

Dr. Gottesman felt that although the guidance document referred to experiments under Appendix L, the types of questions posed in the document would be pertinent to the review of releases involving microorganisms or other plants. Dr. Lacy agreed.

Dr. McKinney said formulating concrete inflexible rules is a gross error as RAC operates in a dynamic area.

Dr. Tolin, the U.S. Department of Agriculture (USDA) liaison representative to RAC and a member of the Working Group on Release into the Environment, said the language of the guidance document is consistent with USDA's role in the release of plants. She said USDA will continue to work with RAC in the evolution of this guidance.

Dr. Pimentel said the document is very good. He suggested that other animal population monitoring also be added to item C-2-d which discusses monitoring of insect populations and disease.

Mr. Mitchell noted that at the last RAC meeting, Dr. Martin Alexander had raised some points; he asked Dr. McGarrity if these points had been discussed by the working group. Dr. McGarrity replied that Dr. Alexander's comments were discussed both at the April 9 and May 31, 1984, working group meetings.

Mr. Mitchell recognized Mr. Jeremy Rifkin. Mr. Rifkin said he agreed the guidance document was a very good beginning. He said that "there should be some minimum standards and methodology and protocol to look over deliberate release experiments."

Mr. Rifkin said he had learned from Dr. McGarrity's presentation the working group would broaden its scope to deal with microorganisms. He said:

"...it seems to me that it'd be appropriate to develop criteria across the board with a universal standard dealing with both plant release and microbes."

Mr. Rifkin said "I'm confused about a few things and I'd like some clarification." He noted the working group had stated that "the proposals so far submitted for their consideration have omitted information that is considered minimal and essential...."

Mr. Rifkin said:

"...what concerns me for today is the proposals this afternoon. One deals with a plant release into the environment and one deals with a microorganism. If it's true what this working group is saying, that the minimum standards--the minimum and essential standards--have not yet been developed to consider proposals and approval of proposals, then I find it hard-pressed to understand how two proposals can be coming up today, one for plant release and one for a microorganism, that have not been subjected to those minimum standards."

Mr. Mitchell suggested Mr. Rifkin's comments were out of order at this time and would be more appropriate when the two proposals were considered in the afternoon.

Mr. Rifkin asked when "the overall standards and procedures and protocols for microorganisms" will be submitted to the RAC for its review and approval. Dr. McGarrity said the "guidance document" for microorganisms was in a preliminary stage, but no definite time schedule could be given.

Dr. Gottesman said Mr. Rifkin confused RAC's ability to review a proposal with the concept of a guidance document for submitters which tells an investigator coming to RAC with a proposal the type of information to submit. Without such guidance, an investigator might overlook information RAC considers important; and RAC may have to send the proposal back to the investigator for more information. Dr. Gottesman said RAC has followed this later procedure in evaluating proposals and will continue to do so if it is not satisfied with the information submitted to it. Dr. Gottesman said in no situation has RAC voted approval of a project without concluding it had adequate information. Dr. McKinney agreed, citing a number of instances when requests were returned to the submitter for additional data.

Mr. Rifkin asked one additional question. He said:

"Assuming that the committee votes in favor of these recommendations this morning and assuming it's approved by the Director of the National Institutes of Health, was there any discussion in the meetings, or perhaps some discussion now, about whether it would be appropriate to wait until there is a formal approval by the NIH before considering proposals that would fall under this? What I'm very concerned about is the wording, and maybe someone can clarify it, that said that the proposals--and I assume all of them--submitted so far to the group

have omitted information that is considered minimum and essential for their approval, and if that's the case I'm wondering if there's been any discussion as to whether this should proceed by a vote and by the Director okaying it before proposals coming up to the RAC are being considered?"

Dr. Gottesman replied that Mr. Rifkin was misconstruing the statement about omitted information. What this statement referred to is that the earliest submissions did not contain as much data as the Plant Working Group would like. It asked for more data; it got the data. It considered those proposals only after the data were supplied and that continues to happen in the review process. The guidance document for future submissions should in no way inhibit the review of individual proposals already submitted.

Dr. Gottesman moved that RAC accept the guidance document as a working document for investigators preparing submissions under Appendix L. Dr. Fedoroff seconded the motion.

Dr. McKinney asked why the phrase "if feasible" was included in the language of item C-1. He suggested the words "as appropriate" be substituted for "if feasible." Dr. McGarrity replied that this language was included because if an investigator were studying plants having a long generation cycle such as pine trees and had to follow the requirement for collecting data for two generations, the investigator would start the experiment as a graduate student and complete it well beyond Social Security age. The phrase "if feasible" was incorporated to provide flexibility in this respect.

Dr. McKinney replied that the words "as appropriate" met these concerns more appropriately than the words "if feasible." In his interpretation, "if feasible" suggests that if an institution does not have the in-house capability to generate the requisite information they can forget about it. He suggested the motion be amended to substitute the words "as appropriate" for the words "if feasible." Dr. Gottesman accepted Dr. McKinney's suggestion to amend the language as did the seconder of the motion, Dr. Fedoroff.

Dr. Walters suggested the language of the guidance document be published as information in the Federal Register.

Dr. Pimentel suggested the language of items C-2-d be amended to mention monitoring of animals and to read as follows:

"d. specify plant monitoring procedures: frequency; types of data to be obtained, including leaf, seed, fruit, or root characteristics; disease, insect and other animal population monitoring;"

Drs. Gottesman and Fedoroff said they would accept Dr. Pimentel's suggestion as they saw this document as a working guidance document for submitters under Appendix L. If animal population monitoring is appropriate for a particular experiment the investigator should submit plans for such monitoring. If on the other hand it is irrelevant, the investigator need not develop such plans.

Dr. Sharples suggested the term "proposed guidance" be substituted for the word "guidelines" in the title so the guidance document would not be confused with the NIH Guidelines for Research Involving Recombinant DNA Molecules.

Dr. Miller said the guidance document is analogous to a FDA document entitled Points to Consider in the Production and Manufacture of Pharmaceuticals Using Recombinant DNA Technology. He suggested the term "Points to Consider" has no regulatory connotation and might be an appropriate title for the guidance document. Dr. Gottesman accepted Dr. Miller's suggestion as did Dr. Fedoroff.

Dr. McKinney suggested the word "requirements" be changed in the last sentence of paragraph two. Dr. Gottesman amended her motion to change this sentence to read: "Information to be submitted should include, but not be limited to:" Dr. Fedoroff agreed.

Dr. Vidaver suggested the term "as appropriate" be added to the language of item C-2-d as monitoring procedures may not be necessary in every case. Drs. Gottesman and Fedoroff agreed.

By a vote of twenty-two in favor, none opposed, and no abstentions, the motion as amended was carried. The document as endorsed by the RAC appears as Attachment II.

VI. PROPOSAL TO CLONE SHIGA-LIKE TOXIN GENE FROM E. COLI

Dr. Gottesman introduced the proposal (tabs 1153, 1156/II, 1162, 1165, 1168, 1170) of Drs. Alison O'Brien and Randall Holmes of the Uniformed Services University of the Health Sciences (USUHS) to clone at P3 containment the Shiga-like toxin gene of E. coli in E. coli K-12 host-vector systems. Shiga-like toxin has activity similar to the activity of Shigella dysenteriae toxin.

Dr. Gottesman reviewed the history of the proposal. In their first submission in September 1982, the investigators proposed to clone the Shiga-like toxin gene in E. coli EK1 host-vector systems using plasmid, cosmid, or lambda cloning vectors. In support of their proposal, Drs. O'Brien and Holmes offered the following arguments:

(1) Clinical isolates of E. coli have already been demonstrated to elaborate large amounts of toxin indistinguishable from that produced by Shigella dysenteriae 1 (Shiga). Therefore, the genes for Shiga-like toxin production are present in the E. coli gene pool found in nature.

(2) Human volunteers fed large numbers of Shigella dysenteriae 1 organisms that produced Shiga toxin but could not colonize the bowel did not become ill. Therefore, any accidental ingestion of the organism to be manufactured, a toxin-producing E. coli K-12

strain that cannot colonize the human intestinal tract, would pose little hazard to man.

(3) Purification of Shiga toxin in several laboratories and E. coli Shiga-like toxin in the investigators' laboratory has not identified any excessive risk from the aerosolization of toxin that probably occurs during the process of toxin preparation. In one laboratory, toxin was isolated from 500 liters of culture with only P1 physical containment.

(4) Shiga toxin is a potent cytotoxin for a subline of HeLa cells (a human cervical carcinoma tissue culture cell line), but the toxin has no effect on many other human, monkey, and rodent tissue culture cells. Therefore, the toxin is quite cell-type specific; and this limited spectrum of activity suggests that it would be non-toxic for most cells in the human body.

(5) Contrary to the old literature, Shiga toxin is not a neurotoxin. By 1955, it was established that the paralysis observed in rabbits and mice (but not monkeys, guinea pigs, hamsters, or rats) when toxin is given intravenously is a reflection of the effect of toxin on the endothelium of small blood vessels, not a direct effect on nerve cells.

This first submission was summarized in the Federal Register of September 22, 1982 (47 FR 41924).

One comment on a related issue was received during the comment period. Dr. K. N. Timmis of the Universite de Geneva suggested that the NIH Guidelines for Research Involving Recombinant DNA Molecules as they relate to the cloning of the Shiga toxin gene be revised. Dr. Timmis argued that Shigella and Escherichia are closely related, and that the NIH recognizes the high degree of relatedness by including these two genera in Sublist A, Appendix A, of the NIH Guidelines. Dr. Timmis argued, therefore, that no NIH review should be required (as now specified by Section III-A and Appendix F) when the Shiga toxin gene is to be cloned in E. coli K-12.

The RAC discussed the request submitted by Dr. O'Brien at the October 25, 1982, meeting. The committee, by a vote of twelve in favor, none opposed, and one abstention, recommended that the initial experiments be performed under P4 + EK1 containment conditions. The NIH accepted the RAC's recommendation that P4 + EK1 containment is adequate to contain safely the experiments proposed by Drs. O'Brien and Holmes and appropriate language was added to Appendix F of the NIH Guidelines.

In December 1983, Drs. O'Brien and Holmes requested reconsideration of containment levels in view of information which had recently become available. They requested approval at the P2 level of physical containment for the following reasons:

(1) Epidemiology studies have been performed on over 150 E. coli strains isolated from human and animal stools. These have shown that the majority (80%) of the strains made detectable levels of Shiga-like toxin. Moreover, four of four substrains of the well-characterized bacterium E. coli K-12 were shown to make low levels of the toxin. Thus, cloning of the Shiga-like toxin gene from clinical isolates of E. coli will not involve the introduction of a "foreign" toxin into the organism.

(2) Production of low levels of Shiga-like toxin was observed in 2 of 15 normal human gut flora E. coli strains from asymptomatic infants.

(3) Strains of Vibrio cholerae and Vibrio parahaemolyticus were tested and shown to produce the Shiga-like toxin. Thus, the gene(s) for Shiga-like toxin are present in naturally occurring isolates of the family Vibrionaceae and not restricted to the Enterobacteriaceae. In volunteer studies, some of the strains of V. cholerae that produce Shiga-like toxin did not cause disease. Therefore, the ability to produce Shiga-like toxin is not equivalent with virulence in humans challenged by the oral route.

(4) Phages from two clinical isolates of E. coli have been shown to control high-level production of Shiga-like toxin in E. coli K-12 host strains by phage conversion. Thus, either the structural gene(s) for the Shiga-like toxin or regulatory genes that control high-level production of the toxin are present on wild-type phages from clinical isolates of E. coli. In this sense, "cloning" of genes that affect production of Shiga-like toxin onto phage genomes has already occurred in nature.

In addition, the U.S. Cholera Panel of the National Institute of Allergy and Infectious Diseases (NIAID) recommended that NIH reconsider the ban:

> "...on Shiga toxin cloning experiments in containment facilities other than P4. This strict requirement will prevent most laboratories from deleting the Shiga gene from candidate V. cholerae and ETEC vaccine strains. Shiga toxin is now found in many nonpathogenic E. coli, including the common vector host, E. coli K-12."

The request for reconsideration was published in the January 5, 1984, Federal Register (49 FR 696). During the comment period, a letter was received from Dr. Werner Arber, the chairman of the Swiss Commission for Experimental Genetics, which is in charge of questions related to research involving recombinant DNA molecules. Dr. Arber wrote that a Swiss ad hoc committee of experts requested by the Commission for Experimental Genetics had reviewed proposed research involving cloning of the Shiga toxin gene in an E. coli host-vector system. Dr. Arber wrote this committee had concluded that:

"Work with recombinant DNA could not be expected to present a more severe biohazard than work with the natural pathogens...recent investigations had shown that a number of bacterial strains related to Shigella, in particular E. coli strains, carried genes homologous to the gene for Shiga toxin...although Shigellosis is a serious disease, it does not represent a serious danger for an epidemic."

A letter from Dr. Kenneth Timmis of the Universite de Geneve said:

"An ad hoc committee of medical microbiologists specifically constituted in Switzerland to evaluate the possible danger of cloning in E. coli K12 the gene for Shiga toxin, concluded that the experiment represented no greater danger than did work on Shigella itself and, as a result, recommended P2/EK1 containment conditions.... A different committee of medical microbiologists set up for the same purpose in Western Germany arrived at precisely the same conclusion."

The RAC reviewed the proposal of Drs. O'Brien and Holmes at the February 6, 1984, meeting. By a vote of nine in favor, five opposed, and four abstentions, the RAC recommended that Drs. O'Brien and Holmes and coworkers be allowed to proceed with cloning the gene for Shiga-like toxin under P2 physical containment conditions in E. coli K-12, restricted to using EK2 plasmid vectors, commencing first with the use of pBR325 and pBR322 and proceeding to other EK2 plasmid vectors only if those are unsatisfactory.

By a vote of eight in favor, four opposed, and five abstentions, the RAC passed the same motion but with the names of the investigators deleted from the motion.

It has been the practice of NIH not to accept RAC recommendations that do not indicate a clear consensus. Accordingly, NIH did not accept the RAC recommendations offered at the February 6, 1984, meeting. The investigators have approval, however, to conduct these experiments at the P4 level of containment under their previous permission which appears in the Guidelines (48 FR 24569) under Appendix F-IV-H.

In a letter dated April 4, 1984, Drs. O'Brien and Holmes asked the RAC to address the following specific issues:

(1) That the containment condition required for cloning of the intact structural gene(s) for Shiga-like toxin E. coli into E. coli K-12 be reduced from P4 + EK1 to P3 + EK1.

(2) If the investigators are successful in cloning the structural gene(s) for Shiga-like toxin and if they can document that the amount of toxin produced by the clones is no greater than the amount made by highly toxinogenic clinical isolates of E. coli (i.e., approximately 10^7 50% cytotoxic doses/mg protein in cell lysates and 10^6 50% cytotoxic doses/ml in culture supernatants when bacteria are grown in iron-depleted glucose syncase media),

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they request permission to remove such clones from the original containment conditions and to perform subsequent work with them under P1 + EK1 conditions.

(3) If they can identify nontoxinogenic fragments of the structural gene(s) for Shiga-like toxin, the investigators request permission to:

(a) Remove any such cloned nontoxic fragments (generated during the search for clones that contain intact toxin structural genes) from the original containment conditions to work with them under P1 + EK1 conditions; and

(b) Directly clone any such nontoxic fragments into E. coli K-12 under P1 + EK1 conditions.

(4) If the structural gene for Shiga-like toxin is shown to be present in a specific bacteriophage genome and its physical location is determined, then they request permission to:

(a) Remove from the original containment conditions any clones of fragments of phage genome (generated during the process of obtaining cloned toxin structural genes) that do not correspond to toxin structural genes and to work with them under P1 + EK1 conditions; and

(b) Directly clone any fragments of the phage genome that do not correspond to toxin structural genes into E. coli K-12 under P1 + EK1 conditions.

(5) If in future experiments the investigator can isolate nontoxinogenic alleles of the structural gene(s) for Shiga-like toxin by transposon mediated mutagenesis (insertional inactivation) or by chemical mutagenesis, they request permission to clone these nontoxinogenic alleles of the toxin structural gene(s) into E. coli K-12 under P1 + EK1 conditions.

Dr. O'Brien and coworkers supplied additional data in support of these requests.

Dr. Gottesman said that at the February 6, 1984, RAC meeting, she had voted against the motion to lower containment from P4 to P2 because she felt certain questions had not been fully addressed. Her perception of the sentiment of the committee at that meeting, however, was that RAC overwhelmingly favored the motion in spite of the split vote. She felt the split vote partially reflected a disagreement over whether the motion should provide an exclusive approval for Dr. O'Brien's group.

Dr. Gottesman said subsequent to the February 6 RAC meeting, Dr. O'Brien had submitted a revised proposal on April 4 and that NIH had convened the

RAC Working Group on Toxins on May 11, 1984, to review the new proposal in the light of available scientific data on Shiga toxin. Dr. Gottesman said a great deal of discussion occurred at the working group meeting. This discussion clarified the scientific issues and resulted in working group recommendations to RAC on Dr. O'Brien's April 4, 1984, proposal.

Dr. Gottesman said these recommendations were unanimously approved by the working group and represent a consensus between individuals holding very different points of view. She strongly urged the RAC to accept the working group recommendations.

Dr. Gottesman said the first request of Dr. O'Brien's April 4 proposal was to lower containment conditions for cloning the intact structural gene(s) for Shiga-like toxin of E. coli into E. coli K-12 from P4 + EK1 to P3 + EK1. Dr. Gottesman said this proposal was accepted by the Working Group on Toxins on the basis of two sets of data:

(1) The data generated through experiments with 140 human volunteers fed Shiga toxin-producing Shigella lacking invasive characteristics. No disease symptoms were observed in 139 individuals; in one individual, the strain reverted to an invasive form and the volunteer developed shigellosis. Since E. coli K-12 neither adheres nor is invasive, no disease should be caused by E. coli K-12 containing the Shiga toxin gene.

(2) The evidence generated by Branham, Dack, and Riggs which shows that large amounts of Shiga toxin instilled directly into monkey intestinal pouches has no effect.

Dr. Gottesman said that in the worst case scenario, in which all the E. coli in the human intestine (estimated to be 10^9) were expressing the Shiga toxin gene on a high expression, high copy number plasmid, one milligram of toxin might be produced in the human gut. This amount is roughly equivalent to approximately 14,000 lethal doses for humans if the toxin were to be administered parenterally. However, Branham, Dack, and Riggs had administered 20,000 lethal doses enterally to monkey intestinal pouches with no observed effect.

In regard to the second item of Dr. O'Brien's April 4 letter requesting lowering of certain characterized clones to P1 + EK1 conditions, Dr. Gottesman said the working group recommends modifications in the request. The working group recommends that host-vector systems expressing the Shiga toxin gene may be removed from P3 to P2 containment conditions under the following conditions:

(1) That the amount of toxin produced by the modified host-vector systems be no greater than that produced by the positive control strain 933 E. coli 0157H7, grown and measured under optimal conditions; and

(2) The cloning vehicle is to be an EK1 vector preferrably belonging to the class of poorly mobilizable plasmids such as pBR322, pBR328, and pBR325.

Dr. Landy asked if the working group recommendation specified that both the host-vector system and strain 933 E. coli 0157H7 were to be grown under optimal conditions. Dr. Gottesman replied that both strains should be grown under optimal toxin producing conditions.

Dr. Gottesman said the working group recommended approval of the third item of the April 4 request with the clarification that the modified organism will not contain overlapping fragments which together would encompass the structural gene(s). This specification will eliminate the possibility that the structural gene might be regenerated through recombinational events.

In regard to the fourth item in the April 4, 1984, proposal, Dr. Gottesman said it was the consensus of the working group that these experiments would not fall under Appendix F of the NIH Guidelines, and no action need be taken by the RAC.

In regard to the fifth item in the April 4, 1984, letter from Drs. O'Brien and Holmes, Dr. Gottesman said it was the consensus of the group that no working group could predict all potential scenarios; thus, each specific nontoxinogenic allele should be considered individually on a case-by-case basis. A system is in place within the NIH to perform this type of evaluation, so no specific action need be taken by the RAC.

Dr. King Holmes said the proposed research is extremely important and should be pursued. He had, however, several concerns which he felt should be addressed: (1) He noted that only four individual animals of one primate species had been tested by Branham, Dack, and Riggs. He asked whether primate species might differ in their response to the toxin. (2) He also questioned the calculations developed by the working group in a worst case scenario; he wondered whether this scenario would correspond to the in vivo situation. (3) He noted that data presented at an earlier RAC meeting by Dr. O'Brien suggested a toxin dose-effect; i.e., E. coli isolates from patients who have hemorrhagic colitis produced more toxin in vitro than did E. coli isolates from patients who did not have hemorrhagic colitis. (4) He questioned what would be the effect of feeding "non-healthy" individuals E. coli K-12 producing Shiga toxin.

Dr. Holmes felt the apparent lack of toxicity for intestinal epithelial cells is not entirely reassuring in terms of toxicities for other epithelial cell types such as HeLa cells. He pointed out that the toxin is presumed to be toxic for endothelial vascular cells. He asked what would be the effect on humans if toxin producing E. coli is inhaled? What if toxin producing E. coli colonizes the skin or urogenital tract?

Dr. Holmes questioned the effect the toxin might have on corneal or conjunctival cells in neonates born vaginally of women vaginally colonized by E. coli producing Shiga toxin. What might be the effect on the endocervix or endometrium of women vaginally colonized by E. coli producing the toxin? What would be the effect on the male whose prostate might be colonized?

Dr. Holmes questioned the language of the third recommendation which specifies that the modified host-vector system will not contain overlapping fragments which together would encompass the structural gene(s); he noted that E. coli K-12 host-vector systems may contain a chromosomal gene encoding Shiga toxin.

Dr. Holmes said he was not persuaded that the proposed experiments require an Arms Control Impact Statement (ACIS) as argued by Mr. Rifkin in his May 15, 1984, letter. Dr. O'Brien's proposed experiments are NIH funded and will be performed by civilian investigators associated with the Uniformed Services University of the Health Sciences (USUHS) medical school. He said he was not persuaded that the affiliation of the investigators with USUHS constitutes a reason per se for requiring an ACIS.

Dr. Holmes suggested the issue as he saw it is not whether an ACIS is necessary for this particular experiment but whether any ACIS might be needed for toxin related recombinant DNA experiments in general.

Dr. Levine pointed out that when the Working Group on Toxins was constituted in the spring of 1981 to evaluate the cloning of toxin genes, it was clear that experiments involving the cloning of the gene encoding botulinum toxin presented a real concern. Botulinum toxin is an exotoxinosis; i.e., the pure toxin if imbibed or ingested orally causes illness. Tetanus toxin also presents a real concern. Shiga toxin, on the other hand, is a very potent toxin when administered parenterally; however, there is no evidence epidemiologically or pathophysiologically that Shiga toxin is an exotoxinosis. In 1981 in discussing the appropriate category for experiments involving cloning of the Shiga toxin gene, the Working Group on Toxins was divided. Some individuals said these experiments should be in the same category as experiments involving the gene for tetanus toxin; this position was based on consideration of Shiga toxin's pharmacological potency. Others felt Shiga toxin should be in a separate category on the basis of epidemiological evidence. As the hour was late, Shiga toxin was assigned to the same category as botulinum and tetanus toxin pending further information. Dr. Levine said most of the Working Group on Toxin members who participated in the May 11, 1984, meeting were members of the working group which in the spring of 1981 drew up Appendix F to the NIH Guidelines. These individuals, thus, had the opportunity at the May 11, 1984, meeting to review additional data concerning Shiga toxin and to offer recommendations. Dr. Levine pointed out that Swiss and West German committees of experts have suggested experiments involving cloning of the Shiga toxin gene be permitted at no higher than P2 + EK1 containment. He said the recommendations of the RAC Working Group on Toxins in contrast represent a very conservative attitude towards the cloning of the Shiga toxin gene. He urged the RAC to accept the working group recommendations.

In response to Dr. King Holmes' stated concerns, Dr. Levine said the Working Group on Toxins, in devising its guidelines for Appendix F, had considered toxicity to primates to be of paramount importance and more relevant than data generated with 40 guinea pigs or 40 mice. He emphasized that the primate data of Braham, Dack, and Riggs show that 20,000 monkey parenteral lethal doses will not cause adverse effect when administered by means of an intestinal pouch.

Dr. Levine said he did not believe E. coli would present a problem by colonizing the skin or peritoneal areas; if E. coli is going to present a problem, it will present a problem in the gut as the numbers of E. coli in the gut are orders of magnitude greater than in other areas of the body.

Dr. Levine said that E. coli strains which cause hemorrhagic colitis, such as 933 E. coli 0157H7, are smooth E. coli strains capable of colonizing the human gut. These strains also have other virulence factors. Nevertheless, these strains are not widespread pathogens. He argued that if strains such as 0157H7 which possess so many virulence characteristics are not widespread pathogens, it is inconceivable that a rough E. coli strain, such as E. coli K-12 which does not colonize or possess virulence factors, would become a widespread pathogen.

Dr. Levine said the infinitesimal risks perceived to be associated with cloning the Shiga toxin gene in E. coli K-12 must be weighed against the actual benefits. He said research with the Shiga toxin gene is very important to the development of a cholera vaccine. He explained that live attenuated cholera vaccines which lack cholera toxin are a major step forward in controlling cholera by immunoprophylaxis. These vaccines, however, still cause a mild diarrhea in perhaps a third of the recipients. Thus, this vaccine is not sufficiently attenuated for public health use. Dr. Levine said the mild diarrhea may be explained in two ways: (1) the diarrhea is a response of the intestine to colonization by the live bacterial strain, or (2) other diarrhea-causing toxins may be produced by the live attenuated strain. Dr. O'Brien and her coworkers have shown that some cholera vaccine strains do produce Shiga toxin. Shiga toxin thus may play a role in causing the mild diarrhea associated with the live attenuated cholera vaccine strains. This possibility must be tested by cloning the Shiga toxin gene and deleting it from the vaccine strains. Delaying this research will adversely affect public health.

Dr. Holmes asked Dr. Levine to explain why if non-invasive V. cholerae vaccine strains may cause Shiga toxin induced diarrhea, would there not be similar concerns about an E. coli strain producing Shiga toxin? Dr. Levine replied that to be a concern the bacterium must possess accessory virulence properties. These virulence properties need not include invasiveness; the organisms must, however, possess characteristics that maintain the bacteria in a special proximity to the intestinal cells. Dr. Levine said the V. cholerae vaccine strains colonize the small bowel in contrast to E. coli K-12 strains which will not colonize the small bowel.

Dr. Clowes said at the February 6 RAC meeting he had supported the motion to lower containment requirements to P2 because: (1) E. coli and Shigella exchange genetic information in nature, and (2) other virulence factors in addition to toxin production are necessary for pathogenicity. He said he had abstained during the vote, however, because he felt the language of the motion was vague. Dr. Clowes said he supported the current recommendations of the Working Group on Toxins. However, as E. coli K-12 probably possesses a chromosomal Shiga toxin gene, he would like to suggest that the working group recommendation on item three of Dr. O'Brien's April 4 request be modified to require P2 containment conditions.

Dr. Fedoroff felt P2 containment was not necessary. She pointed out that two recombinational events would have to occur to generate a plasmid vector carrying the full structural gene for Shiga toxin: one recombinational event to integrate the plasmid into the chromosome, and a second to return the plasmid to the extrachromosomal state.

Dr. McKinney said Dr. Clowes' suggestion satisfied Dr. Holmes' concern regarding inhalation exposure to Shiga toxin-producing E. coli since P2 reduces the probability of exposure by aerosol. He supported Dr. Clowes' suggestion.

Dr. Gottesman said she wished to respond to certain of Dr. Holmes' concerns. She reminded the committee the proposed research with the Shiga toxin structual gene is to be performed under P3 containment with E. coli K-12 host-vector systems. P3 containment conditions severely limit the possibility of the organism escaping. In addition, the host in this case would be E. coli K-12 which is a debilitated strain. In addition, Dr. Gottesman argued that Shiga toxin exists in E. coli strains in nature; thus, the only way in which a novel organism might be produced by recombinant DNA techniques is if the plasmid construct produces higher levels of toxin than strains in nature. Dr. Gottesman felt these considerations and the primate data indicating that Shiga toxin is not toxic when delivered in the gut address most of the concerns.

Dr. Gottesman moved that RAC recommend experiments involving the cloning in E. coli K-12 of the intact structural gene(s) of Shiga-like toxin of E. coli be permitted at P3 + EK1 containment. This is the first request in Dr. O'Brien's April 4 proposal. Dr. Fedoroff seconded the motion. Dr. King Holmes noted that he would support the motion as he felt the benefits greatly outweigh the risks. By a vote of twenty-one in favor, none opposed, and one abstention, the RAC recommended the motion.

Dr. Gottesman then moved RAC approve the working group recommendation that E. coli host-vector systems expressing the Shiga toxin gene may be removed from P3 to P2 containment under the following conditions:

(1) That the amount of toxin produced by the modified host-vector systems be no greater than that produced by the positive control strain, 933 E. coli 0157H7, grown and measured under optimal conditions; and

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(2) The cloning vehicle is to be an EK1 vector, preferably belonging to the class of poorly mobilized plasmids, such as pBR322, pBR328, and pBR325.

Dr. Fedoroff seconded the motion.

Mr. Jeremy Rifkin was recognized and said he felt that a critical turning point has been reached with this technology. He thought this turning point similar to the turning point in the nuclear technology discussions where it became very obvious there was a convertibility between the peaceful use of nuclear technology and its possible military applications. Mr. Rifkin felt this convertibility was especially obvious in relation to the use of plutonium in the nuclear energy industry and its use in military weapons.

Mr. Rifkin said that in the last few months several disturbing events occurred: (1) the Wall Street Journal published a seven part series on possible military applications of genetic engineering in the Soviet Union; (2) the American Association for the Advancement of Science held a panel on biological warfare at their annual meeting at which a spokesperson from the Defense Information Agency pointed out the convertibility between peaceful uses of this technology and military applications; and (3) Environmental Action and the Foundation on Economic Trends joined in releasing to the public a mathematical model from the leading Soviet mathematical modeler of epidemiological studies. This scientist is concerned that the mathematical model he developed for tracing and tracking viruses could be used for military purposes.

Mr. Rifkin said he was curious about the interest in Shiga toxin because it was his understanding that this particular form of dysentery is not found in any significant way in the United States but is pandemic to the five countries of Central America. He said:

"...it doesn't take much intelligence to understand that it would be very helpful to have such a vaccine, if for no other reason, to inoculate U.S. ground troops."

He added that:

"U.S. ground troops having that kind of vaccine would be able to be in a position to be deployed in those five Central American countries with the protection of that vaccine."

Mr. Rifkin suggested that RAC:

"...postpone consideration of this experiment and similar experiments by DOD or DOD-related institutions until such time as another agency, the Arms Control and Disarmament Agency, complies with the ACIS requirements."

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Mr. Rifkin called the attention of the committee to the letter from Dr. Jay Sanford, President of the USUHS (Attachment III), which states that the Department of Defense (DOD) does not believe these experiments will have a significant impact on arms control and disarmament. Mr. Rifkin said that the Arms Control and Disarmament Agency is the agency which has to deal with it, not the DOD.

Mr. Rifkin suggested that RAC discuss setting up a RAC subgroup to:

> "...take a look at this whole area of convertibility of toxins from peaceful uses to military uses and to initiate a very exhaustive study, complete with recommendations and findings, to bring back to this committee for discussion at a future date."

Mr. Rifkin also suggested that the subgroup:

> "...look at all of the ways that we might deal with controls, regulations, protocols, and procedures dealing with this whole question of toxins used for domestic purposes versus military."

Dr. Levine said he wished to offer a few clarifications. He explained that:

> "Shiga toxin was originally isolated from a serotype of Shigella called Shigella dysenteriae-1, or Shiga. That particular organism caused pandemic dysentery in Central America from 1968-1970. There no longer is a pandemic in Central America. There hasn't been for many years. In fact, it's an uncommon endemic organism in Central America. Shigella dysenteriae-1, amongst all Shigella, amongst all bacteria, is one of only a handful of organisms that are capable of exhibiting pandemic spread, and that occurs every couple of generations interspersed widely throughout the world. One does not really know why it turns up. There was a similar large epidemic in Bangladesh in the 1970s, for example; there was one 15 years earlier in East Africa. There is no Shiga dysentery pandemic in Central America now....
>
> "The genes, however, that Shigella dysenteriae-1 have, we now recognize are in all Shigella, or apparently all Shigella, because all Shigella serotypes that have been looked at are now found to produce this toxin. And what's much more important, E. coli which everybody in this room has in their intestine, some E. coli can produce lots of Shiga toxin....
>
> "The last point I would make, Mr. Chairman, is that it bothers me, as a health worker and health professional interested in geographic medicine and tropical pediatrics, to have such great emphasis put on one aspect of warfare when there's another war out there and it's a war that I'm involved in fighting in a different way and that is a war against disease, and that's also a real war, and that's taking place now, that's not hypothetical. Shiga dysentery does cause disease, cholera causes disease. There are many, many--there are millions of children--that die of these diseases throughout the world. That's war, and we need

every armament we have against that war. Without question, nefarious individuals in many countries can take not only guns and arms and such explosive armaments, but nefarious individuals can use biological means and chemical means and apply them in warfare without question. But they don't need to clone Shiga toxin to do this. My lord, there are so many nasty agents that exist for the potential for warfare that we know about. But there's another war out there and I think it's our primary responsibility to come up with the best armaments to fight that other war."

Mr. Rifkin said he totally agreed that:

"...we have a responsibility to develop vaccines that are going to be helpful in dealing with some of these dreaded diseases. All I'm suggesting at this point is that we're at a stage where there is a convertibility with toxins for military purposes, and just as we're interested in solving the problem of diseases, shouldn't we be interested in setting down some guidelines, and protocols, and procedures for the potential convertibility of this technology...."

Mr. Rifkin asked if there was:

"...any room for discussion at this committee of the NIH for taking a look at how toxin-related experiments might be somehow used for military purposes? If not, I won't bring it up again, if you think that there is no room for this committee, or the NIH, to look into this matter in any way, shape, or form about the convertibility. I will not bring it up again if you so decide that that's your--the NIH's--position."

Dr. McKinney said he:

"...would make the observation, Mr. Chairman, that if indeed our concern would be predicated on convertibility of any technology to ultimate use in warfare that we should have started with the invention of the wheel and that we would, in fact, cease to do any and all research in the world because of the potential for converting any new technology to ultimate warfare use."

Dr. McKinney said he wished to comment on the materials which accompanied Mr. Rifkin's letter of May 15, 1984. He said he had found a number of gross technical errors in this material. He cited Mr. Rifkin's statement that RAC is authorizing experiments. Dr. McKinney said RAC does not "authorize" experiments, rather it is an advisory body to the NIH. It is the prerogative of the NIH to accept or reject RAC's recommendations. Dr. McKinney felt the inappropriate use of the word "authorize" conveys to the public a false impression of RAC's function.

Dr. McKinney said he could not accept Mr. Rifkin's position that RAC is a participant in the potential convertibility of a technology to military applications. He said such a potential exists with any technology. The

primary role of RAC, however, is to serve the public interest. In this service, concrete measures to control disease have precedence over hypothetical considerations which might be raised over what somebody might do someday.

Dr. Landy said he was personally offended by Mr. Rifkin's implication that American researchers would not feel compelled to research diseases that are not endemic to the United States.

Dr. Miller underscored the public health importance of the research proposed by Dr. O'Brien. He urged RAC to recommend conditions which would permit this research to proceed. Dr. Miller felt the:

> "...issue of convertibility to biological warfare is really...not an issue at all, but rather...a manifestation of what the British journal Nature in the May 24th issue alluded to in describing Mr. Rifkin as someone whose nuisance to substance ratio is high."

Dr. Rapp said a toxin is one type of virulence factor. If the words "virulence factors" were used instead of the word "toxin", many experiments with important health problem applications would be part of the convertibility discussion.

Dr. Rapp strongly supported Dr. Landy's comments. He offered as an example the research being conducted in the U.S. on malaria. He did not think the U.S. was going to invade West Africa because U.S. researchers are studying malaria. Malaria is an important international health problem and most U.S. researchers consider themselves international scientists attempting to solve world health problems. Dr. Walters agreed.

Dr. McGarrity pointed to Appendix F as evidence that RAC and the Working Group on Toxins have deliberated long and hard in considering recombinant DNA experiments involving toxin genes.

Dr. Gottesman said the concern that this research might be converted to uses scientists would not approve is one reason scientists began the process of evaluating applications of the recombinant DNA technique. This concern was discussed at Asilomar. The RAC meets in open session to keep the public aware of the issues.

Dr. Gottesman said she was bothered a great deal by Mr. Rifkin's implication that these experiments are more likely to be misused because the investigators are associated with USUHS. She said this is "guilt by association." She rejected this implication and urged RAC to approve the working group recommendations concerning Dr. O'Brien's April 4, proposal.

Mr. Rifkin said:

> "...it's rather disingenuous for the committee to suggest that I'm only interested in diseases that affect the United States of America and,

therefore, don't care about diseases that affect the world. I think if anybody is familiar with my writings of books over the years you know that's just not true."

Mr. Rifkin said:

"...the real question here that I think that we have to deal with is a question that's been raised not just by me; it's been raised in several forums. If you get a chance to read, for example, the Bulletin of Atomic Scientists, which is rather a distinguished journal of science, you'll find there was a long article in the November issue by Dr. Sinsheimer of the University of California and another historian where they raised some problems about convertibility and raise some very specific suggestions about what might be done by various Government agencies to try and address this issue, yet it still has not been addressed in this committee as of today."

Mr. Rifkin added that:

"In terms of a nuisance factor...We are all American taxpayers. We are citizens. We come in front of this committee both as professionals and lay people to lay out our concerns. I have legitimate concerns. You might totally disagree with them. You might have a totally different perspective. But we owe it to each other to discuss these and in each case when you have decided and voted I have not said another thing on that particular area. But I will continue to be here if I think that the perspectives that I want covered are not covered by this committee, including this one, and I hope at some point you discuss the convertibility of this technology for military purposes."

It had previously been moved and seconded that the RAC approve the recommendation of the Working Group on Toxins that E. coli host-vector systems expressing the Shiga toxin gene may be removed from P3 to P2 containment under the following conditions:

(1) that the amount of toxin produced by the modified host-vector system be no greater than that produced by the positive control strains 933 E. coli 0157H7 grown and measured under optimal conditions; and

(2) the cloning vehicle is to be an EK1 vector preferrably belonging to the class of poorly mobilizable plasmids such as pBR322, pBR328, and pBR325.

By a vote of twenty-one in favor, one opposed, and one abstention, the RAC accepted the motion.

Dr. Gottesman then moved acceptance of the third item of the April 4, 1984, request, i.e., to remove nontoxinogenic fragments of the structural gene(s)

from P3 to lower physical containment at EK1 biological containment with the stipulation that the modified organism will not contain overlapping fragments which together would encompass the structural gene(s). In response to concerns expressed earlier in the meeting, Dr. Gottesman moved that physical containment be set at P2, higher than the requested P1 physical containment level. Dr. Fedoroff seconded the motion. By a vote of twenty-one in favor, none opposed, and one abstention, the RAC accepted the motion.

Dr. Gottesman felt a motion concerning items four and five was not required, but moved that RAC indicate that items four and five of Dr. O'Brien's April 4, 1984, request do not require RAC action. Dr. Holmes seconded the motion. By a vote of twenty-one in favor, none opposed, and one abstention, the RAC approved the motion.

VII. DISCUSSION OF REPORT "THE ENVIRONMENTAL IMPLICATIONS OF GENETIC ENGINEERING" AND QUESTIONS POSED BY DR. TALBOT

Mr. Mitchell said this discussion involved two related issues (tabs 1148, 1149, 1150, 1151, 1152, 1159, 1160, 1164, 1167, 1172, 1175): (1) the report (called the Gore Report) of the staff of the Subcommittee on Investigations and Oversight of the House of Representatives Committee on Science and Technology; and (2) the questions posed by Dr. Talbot concerning NIH's appropriate future role [Dr. Talbot's questions were also discussed at the February 6, 1984, RAC meeting. The discussion appears in the minutes of that meeting as item X. Questions Concerning Boundaries for NIH and RAC Oversight.]

Mr. Mitchell called on Dr. McGarrity, the Chair of the Working Group on Release into the Environment, to begin the discussion. Dr. McGarrity said he would begin his report with the evaluation by the Working Group on Release into the Environment of the Gore Report and its associated documents.

Dr. McGarrity said the Working Group on Release into the Environment met on April 9, 1984, and considered the Gore Report in detail. He said tab 1151 is the official response of the working group to the recommendations of the Gore Report.

Dr. McGarrity called the RAC's attention to the preamble of the working group response (tab 1151). He said the preamble was based on three important points. These are:

(1) The assumption that RAC at least for the immediate future should continue to review and where appropriate recommend approval of proposals for release into the environment of genetically engineered organisms.

(2) The recombinant DNA technique is only one of many techniques whose products would fall under the general classification of "genetically engineered" organisms. The working group, however, restricted its discussion to recombinant DNA as defined in the NIH Guidelines.

(3) The working group felt strongly that both research and commercial releases of genetically engineered organisms should be subject to review.

Dr. McGarrity then reported on the working group response to each recommendation of the Gore Report. He said the first recommendation of the Gore Report is that:

"The EPA should proceed with its stated intention to extend its authority to include all deliberately released organisms not specifically identified as part of the legal obligation of another agency. In view of EPA's stated conclusion that the Toxic Substances Control Act (TSCA) does provide it with authority to oversee deliberate releases and the fact that Congress intended TSCA to be 'gap filling' legislation, no additional legislation or clarifying amendments are needed at this time. EPA should, however, establish formal communications and agreements with other agencies to ensure that gaps and redundancies in the regulatory structure do not occur. A major goal should be to permit research and commercialization to proceed with minimum interference while adequately addressing environmental and public health concerns."

Dr. McGarrity said the working group refrained from offering any comment whatsoever on this point.

Dr. McGarrity said the second recommendation of the Gore Report is that:

"Until such time as EPA's regulations are promulgated, an interagency task force should be established to review all proposals for deliberate releases. EPA should take the initiative in organizing this panel. The panel should be comprised of representatives from EPA, USDA, NIH, and any other appropriate federal agency or entity directly involved from either the scientific or regulatory perspective. The panel should establish an environmentally oriented risk/benefit assessment program to evaluate current proposals for deliberate releases and to provide a data base for decisions on future releases. The panel should also develop a uniform set of guidelines to govern deliberate releases. The panel should, moreover, serve the function of educating the public about the potential risks and benefits associated with this aspect of biotechnology. Consideration should be given to making this panel a permanent oversight body even after EPA has promulgated regulations to ensure that the broadest possible expertise is brought to bear in overseeing the technology."

Dr. McGarrity said the Working Group on Release into the Environment responded:

"We endorse the concept of a single task force with the responsibility and expertise to consider release of genetically engineered organisms, but for recombinant DNA-containing organisms, we believe the RAC currently best serves this function.

"While there is a need for a set of general principles which should be considered for all deliberate releases, we are skeptical of the feasibility of developing a uniform set of testing requirements for all organisms and all environmental situations. We believe an appropriately constituted review group to consider specific cases will be both flexible and responsive to the particular problems posed by particular releases."

Dr. McGarrity said the third recommendation of the Gore Report is as follows:

"No deliberate release should be permitted by EPA, NIH, USDA, or any other federal agency until the potential environmental effects of the particular release have been considered by the interagency review panel. The panel shall consider the effects of any environmental release, regardless of size or intent. Each agency should evaluate proposals for deliberate releases according to a uniform set of guidelines to be developed by the interagency task force. It is recognized that initially decisions may be made on the basis of incomplete data."

Dr. McGarrity said the working group endorsed one concept in the third recommendation of the Gore Report, i.e., there is a need for a review of environmental data and the effects of any releases. However, the Gore Report is inconsistent because in many sections it states progress in this rapidly developing technology should not be impeded, rather progress should be aided; on the other hand, the report suggests no environmental releases should be performed until an interagency task force reviews releases. The dilemma, however, is that an interagency task force is not in place and functioning.

Dr. McGarrity said the working group response to the third recommendation of the Gore Report is contained in the response of the working group to the second recommendation of the Gore Report: i.e., that environmental releases would be reviewed by RAC and its working groups until such time as another appropriate review mechanism is in place.

Dr. McGarrity said the fourth recommendation of the Gore Report is that:

"The task force should consider the need for oversight of research scale releases and, if appropriate, develop guidelines for reviewing proposals for such releases. The task force should prepare a report containing its conclusions on this matter within 90 days of its establishment. The report should be made available to the Subcommittee."

Dr. McGarrity said the working group replied to the fourth recommendation as follows:

"The Plant Working Group and this working group have contributed to an evolving set of procedures for evaluating experiments with plants and associated microorganisms. This process should continue and be applied to 'deliberate release' of other genetically engineered organisms as well."

Dr. McGarrity said the fifth recommendation of the Gore Report is that:

> "The NIH should cease its practice of evaluating and approving proposals for deliberate releases from commercial biotechnology companies. The NIH should review proposals only from parties engaged in NIH-sponsored research, and refer requests from industry to the appropriate agency."

Dr. McGarrity said the working group rejected the fifth recommendation of the Gore Report. The Gore Report states that it does not wish any of its recommendations to create a oversight vacuum; the working group strongly believes that should NIH cease reviewing proposals there would indeed be a vacuum in the review and evaluation process. The working group feels at present RAC is the group best equipped to conduct reviews.

Dr. McGarrity said the sixth recommendation of the Gore Report is that:

> "The NIH and USDA should revise the membership of their respective Recombinant DNA Advisory Committees (RAC) to include individuals specifically trained in ecology and the environmental sciences."

Dr. McGarrity said the working group response is that:

> "NIH is already responding to this suggestion in three ways: (1) changes in RAC membership; (2) use of ad hoc consultants to the full RAC; and (3) use of environmental experts on working groups of the RAC."

Dr. McGarrity said the seventh recommendation of the Gore Report is that:

> "The General Accounting Office should review the activities of USDA in overseeing biotechnology and evaluate the agency's authority to regulate deliberate releases under all relevant statutes, regulations, and executive orders."

Dr. McGarrity said the working group made no comment on this recommendation.

Dr. McGarrity said in his fours years on the RAC he has been involved in many issues: voluntary compliance, closed sessions, toxins, human subjects, plant applications, and environmental releases. Many letters received indicated that RAC has done a reasonable job over the years. RAC's advantages are that it became involved very early in the recombinant DNA area, it was flexible, and it developed a very good track record. Perhaps RAC's record has now created problems for other agencies as there was probably a tendency to let NIH, which is not a regulatory agency, deal with the issues.

Dr. McGarrity said he applauded the efforts of other government agencies to deal with the issues, and he endorsed the concept of an interagency task force or other appropriate committee to deal with issues in deliberate release. Establishment of an interagency task force is, however, only a recommendation and not currently a reality. He suspected it will take time to develop the necessary committees.

Dr. McGarrity said he and the Working Group on Release into the Environment believe RAC should continue its major functions at least until such time as another appropriate agency or committee comes into existence. He said the future role of RAC will not be decided by RAC members or by scientists but by administrators, policymakers, and the legal system.

Dr. McGarrity then informed the RAC of the responses of the Working Group on Release into the Environment to the questions posed by Dr. Talbot.

Dr. McGarrity said Dr. Talbot's first question is as follows:

> "Should the NIH guidelines be limited strictly to work done in the laboratory? In this case, 'release to the environment' including field tests would fall outside the jurisdiction of the Guidelines."

Dr. McGarrity said the working group responded that the NIH Guidelines should not be strictly limited to laboratory procedures and laboratory studies. The group believed such on action would essentially create an oversight vacuum.

Dr. McGarrity said the second question posed by Dr. Talbot is as follows:

> "Should NIH accept for review only individual proposals funded by NIH or only proposals funded by the Federal government? In this case, review of individual proposals from industry would fall outside the Guidelines."

Dr. McGarrity said the working group felt RAC should review all submitted proposals regardless of the funding source.

Dr. McGarrity said Dr. Talbot's third question asked whether:

> "...all portions of all RAC meetings be open to the public? In this case, NIH could cease to accept any proprietary data for review and such would fall outside the boundaries of the Guidelines."

Dr. McGarrity said the consensus of the working group is that it is proper to hold closed meetings when proprietary data are discussed.

Dr. McGarrity said Dr. Talbot's fourth question asks:

> "Should the NIH Guidelines be limited strictly to biomedical research? In this case, agricultural and other studies would fall outside the jurisdiction of the Guidelines."

Dr. McGarrity said the working group responded that the Guidelines should not be limited only to biomedical research but should apply to all applications.

Dr. McGarrity reported that several criticisms of the Gore Report were raised during the working group discussion. Dr. McGarrity said he thought

the Gore Report was a good beginning; but a number of working group members had problems with inconsistencies, the definitions, the language, and some of the findings and rationale of the report.

Dr. Vidaver concurred with Dr. McGarrity's report of the April 9 meeting of the Working Group on Release into the Environment. She suggested Dr. Brill's response (tab 1159) to the Gore Report be made part of the record. Drs. Fedoroff and Pirone supported Dr. Vidaver's suggestion.

Dr. Scandalios also concurred with Dr. McGarrity's report. He suggested RAC endorse Dr. Brill's response to the Gore Report. Dr. Lacy suggested Dr. Brill's letter be carefully evaluated.

Dr. Tolin endorsed Dr. McGarrity's report. She said she specifically wished to address the sixth recommendation of the Gore Report which suggests that:

> "NIH and USDA revise the membership of their respective Recombinant DNA Advisory Committees (RAC) to include individuals specifically trained in ecology and the environmental sciences."

She stated that USDA does not have an advisory committee comparable to RAC; the USDA Recombinant DNA Committee (ARAC) is a USDA internal administrative committee and its members are appointed by virtue of their position in the USDA administrative hierarchy. Dr. Tolin said the current RAC is composed of experts from many different disciplines and institutions. This interdisciplinary approach is RAC's strength, and USDA endorses this concept.

Dr. McKinney said at the White House level the Chairman Pro Tempore of the Cabinet Council on Natural Resources and the Environment has approved establishing a Cabinet Council Working Group on Biotechnology to undertake a review of the federal regulatory rules and procedures relating to biotechnology. He said the Cabinet Council Working Group might set standards against which an interagency task force might operate. Dr. McKinney felt if the Cabinet Council Working Group is going to develop standards, RAC can anticipate a very long delay before an interagency task force is functioning in reviewing proposals involving release of modified organisms to the environment. He urged NIH to attempt to obtain for RAC a clarification of the anticipated strategy of the Cabinet Council Working Group.

Dr. McKinney said many recent reports dealing with recombinant DNA and biotechnology such as the Gore Report or the Office of Technology Assessment (OTA) report entitled Commercial Biotechnology: An International Analysis have problems defining biotechnology. Dr. McKinney thought a clear definition of what constitutes biotechnology should be developed.

Dr. Henry Miller of FDA said that the Gore Report is a substantially flawed document. He cited one example of the imprecision found in the document. The third recommendation of the Gore Report specifies that:

"No deliberate release should be permitted by EPA, NIH, USDA or any other federal agency until the potential environmental effects of the particular release have been considered by the interagency review panel...."

The report defines genetically engineered organisms very broadly to include not only organisms modified by recombinant DNA techniques, but also organisms modified by techniques such as protoplast fusion, chemical mutation, etc. If FDA were to take the third recommendation of the Gore Report at face value, no FDA approvals would be given for the "release" of live attenuated virus vaccines until reviewed by the new interagency review panel. Many of these vaccines, including live attenuated polio virus vaccine, have been around for a very long time and are produced by conventional, nonrecombinant DNA, genetic engineering techniques.

Dr. Fedoroff said RAC should construct an independent response to the Gore Report. This response should include criticisms of the report such as those noted by Dr. Miller. She did not think the committee should reply to the Gore Report simply by endorsing Dr. Brill's letter, although she thought the letter was excellent.

Dr. Sharples said it would be inappropriate to send to Representative Gore the Brill letter as part of RAC's response to the Gore Report. She pointed out that Dr. Brill is affiliated with industry and not a RAC member. She said she personally disagreed with several of Dr. Brill's comments. For example, she disagreed with Dr. Brill's statement that there are no significant differences between recombinant organisms and nonengineered organisms; she said that some recombinant organisms may possess characteristics such as the ability to transfer gene sequences which nonengineered organisms do not possess. Furthermore, Dr. Sharples felt there was a fundamental inconsistency in RAC endorsing a letter which states "there are no problems" with the fact that RAC exists to evaluate whether there are problems. Dr. Pimentel supported Dr. Sharples position; he suggested that RAC should act in a scientifically sound manner.

Dr. Fedoroff said she did not wish to imply that RAC endorse Dr. Brill's letter in RAC's official response to the Gore Report. She thought RAC should formulate an independent response based on valid criticisms of the Gore Report.

Mr. Mitchell said RAC could proceed in several ways: (1) return the matter to the working group; (2) the Chair could appoint a working group of two or three people to draft a response; or (3) no specific action would be taken other than accepting the response of the Working Group on Release into the Environment.

Dr. McKinney felt any response to the Gore Report should be circulated to all RAC members for comment before finalization as there may be minority opinions.

Dr. Fedoroff asked if RAC's response to the Gore Report would be transmitted to the House Subcommittee on Investigations and Oversight. Dr. Talbot said RAC could ask NIH to transmit the report. He pointed out, however, that RAC minutes are available to the public and authors of the Gore Report are present at this meeting and have heard the discussion.

Dr. Fedoroff felt some public comments reflect an enormous ignorance of RAC procedures. She suggested RAC be more aggressive in disseminating information about how RAC functions.

Dr. Fedoroff moved that a subgroup of the Working Group on Release into the Environment be appointed to formulate a response to the Gore Report. The draft response would be sent to the full RAC for review. Dr. McGarrity seconded Dr. Fedoroff's motion. Dr. Harvin suggested the draft response be discussed at the next RAC meeting.

Mr. Mitchell said the Chair understands Dr. Fedoroff's motion to encompass endorsement of the response of the Working Group on Release into the Environment to the recommendations of the Gore Report. The motion also endorses the views of the working group on the question of RAC's future role.

Dr. Clowes asked if there was any purpose to lumping together the working group responses to the Gore Report with the working group responses to Dr. Talbot's questions. He thought it reasonable to vote on each issue separately. Dr. McGarrity felt the responses to Dr. Talbot's questions bear on the response to the Gore Report. He felt these responses would help convey the sense of the working group regarding the current functions and duties of the RAC.

Dr. Carl Mazza of the Environmental Protection Agency (EPA) said a letter from the EPA Administrator, Mr. Ruckelshaus (Attachment IV), which was being circulated among the assembly, contains Mr. Ruckelshaus' reply to the recommendations of the Gore Report.

Dr. Mazza said he saw three levels of issues in the Gore Report. The first are the scientific questions raised by the Gore Report. There is a great deal of debate about the relevance or accuracy of some of the scientific conclusions; thus, individuals who examine the Gore Report from this perspective view the report negatively.

Dr. Mazza said the second level issues are the specific recommendations of the Gore Report. The Gore Report calls for the formation of an interagency task force and for experimentation in this area to await the formation of the task force. As no task force exists, a person viewing the Gore Report from this perspective would have problems with the report.

Dr. Mazza said the third level issues deal with a series of concerns about coordination between the various Federal agencies, communication between the Federal agencies and the need to gather expertise government-wide. These concerns are: Are current regulatory authorities adequate? Is there adequate coordination among the agencies? Are other mechanisms such as an

interagency review group necessary? Dr. Mazza said the EPA shares these third level concerns; the concern of the Federal government is reflected in the creation and mandate of the Cabinet Council Working Group on Biotechnology. Dr. Mazza felt many of these third level concerns are shared by many people in the assembly and should not be disregarded.

Mr. Mitchell said RAC has considerable experience in the recombinant DNA area and some RAC members are frustrated to learn that some RAC actions have been misunderstood or misconstrued. Mr. Mitchell said no other group of comparable composition or history has existed in the field and RAC's views and opinions should carry a certain weight. Mr. Mitchell said there was a feeling RAC should more forcefully express its views and opinions and get all the facts on the table.

Dr. McKinney said he may have misunderstood, but he thought Dr. Mazza was suggesting RAC not respond to the Gore Report because RAC ran the risk of muddying the waters. Dr. McKinney thought RAC has an obligation to respond as it has expertise, sound information, and experience to contribute. He recalled that in the early history of the recombinant DNA issue a great interest in passing legislation existed in Congress but later gradually disappeared. Now, RAC is going through another cycle because new events have caused people to reexamine how RAC has managed this technology. He felt the valued experience of RAC must be brought to bear on this subject. RAC is and will continue to be an integral part of this debate and must maintain communication and provide input. RAC cannot simply wait to see what happens.

Mr. Nicholas, the Staff Director of the Subcommittee on Investigations and Oversight, said he perceived a defensiveness among RAC members about RAC's role; he did not think the Gore Report was critical of RAC's role. He thought there was a general consensus, in Congress as well as elsewhere, that RAC has done an excellent job. Mr. Nicholas said the question is "where do we go from here."

Mr. Nicholas said the Gore Report was an attempt to create a process to resolve difficult issues. It was widely circulated for comment, and a good scientific discussion by RAC of the issues would be totally appropriate. If the Gore Report may be legitimately criticized for certain statements, the staff of the Subcommittee on Investigations and Oversight deserves the criticism. Mr. Nicholas advised strongly, however, against RAC endorsing the letter from Dr. Brill as: (1) the letter has not been subjected to a critical review, and (2) endorsing the letter imparts an inappropriate tone to the debate. Mr. Nicholas said perspectives such as RAC's should be lent constructively to the process of helping the Federal Government deal with this difficult issue. Mr. Nicholas referred to the motion made earlier in the meeting to append to the minutes of the February 6, 1984, RAC meeting, the ASM reply to Representative Gore concerning the Giles and Whitehead publication. Mr. Nicholas suggested that to establish a viable equal dialogue, Representative Gore's response to the ASM letter should also be made part of the record.

Dr. McGarrity said he wished to place in perspective the responses of the Working Group on Release into the Environment to the Gore Report. The working group took exception to only two of the seven recommendations in the Gore Report; the third recommendation which suggested that field testing experiments should not be approved until an interagency task force is established and the fifth recommendation which suggested that NIH should cease its practice of evaluating and approving proposals for deliberate release from commercial biotechnology companies. As no interagency review task force exists, the working group felt a vacuum would be created if the NIH accepted these recommendations of the Gore Report.

Mr. Mitchell agreed any response RAC would send to Representative Gore must be well considered. The document should address deficient or overlooked topics from a scientific standpoint. RAC should also offer the benefit of its members' feelings, attitudes, and experience in working in this area for almost ten years.

Dr. Fedoroff called the question. By a vote of seventeen in favor, none opposed, and no abstentions, the question was called.

Mr. Rifkin asked to be recognized. Mr. Mitchell said a RAC member had called the question and the RAC had unanimously support of this action. He said he would abide by this vote unless a RAC member wished to appeal his decision. No appeal was made. Dr. Harvin pointed out that several individuals had commented from the floor during this discussion.

Dr. Fedoroff reiterated that the motion is to accept the responses of the Working Group on Release into the Environment to the recommendations of the Gore Report and to direct a subgroup of the working group to compose a document which spells out the rationale underlying those responses. The document should offer an exposition of the criticisms of the Gore Report raised by the working group and the RAC. The document would be discussed by RAC at it next meeting and if adopted by RAC would be communicated to Mr. Gore.

Dr. Fedoroff said she preferred to consider the responses to Dr. Talbot's questions as a separate issue.

By a vote of twenty in favor, none opposed, and one abstention, the RAC accepted Dr. Fedoroff's motion.

VIII. FUTURE MEETING DATES

Dr. Gartland said the next meeting of the RAC would probably be held in mid to late October.

IX. PROPOSAL FROM ADVANCED GENETIC SCIENCES, INC. (OPEN SESSION)

Mr. Mitchell said this agenda item (tab 1155, 1156/V, 1168, 1169) deals with generic issues in the Advanced Genetic Sciences Inc. (AGS), proposal. He said a closed session immediately following the open session would review proprietary information submitted as part of the proposal. Dr. Talbot said a vote on the proposal would be taken during the closed session.

Dr. Vidaver said the AGS proposal to field test deletion mutants of Pseudomonas syringae was originally to be discussed at the February 6, 1984, RAC meeting. A court order, however, prevented discussion of this proposal. [See IX. Announcement Concerning Appellate Court Ruling and Other Announcements of the minutes of the February 6, 1984, meeting.] Dr. Vidaver said the Plant Working Group subsequently transmitted to AGS through the Office of Recombinant DNA Activities its perception that the proposal was deficient. Dr. Vidaver said AGS has now submitted a vastly improved proposal.

Dr. Vidaver said the AGS proposal is virtually identical in concept and scope to a proposal submitted by Drs. Steven Lindow and Nickolas Panopoulos of the University of California, Berkeley, which was approved at the April 11, 1983, RAC meeting. Both proposals seek to ameliorate frost damage to plants caused by ice nucleating bacteria. The principal differences between the proposals are the modified bacterial strain and the test crop.

Dr. Vidaver offered some background information on ice nucleating (INA^+) bacteria. She said a few bacteria can act as catalysts for the transition of water to ice, i.e., they act as ice nuclei. Plants harboring such bacteria will freeze at a higher temperature, a relatively warm -2 to -8 degrees centigrade, than plants that do not harbor such bacteria. Several scientists have hypothesized that INA^- bacteria, i.e., those lacking the property to ice nucleate, will compete with INA^+ bacteria for attachment sites on plants and thus prevent frost injury to the plant. Both growth chamber and field data obtained using non-genetically engineered INA^- bacteria tend to support this hypothesis.

Dr. Vidaver said the majority of ice nucleation active bacteria (INA^+) are identified as Pseudomonas syringae, a highly variable bacterial species. She emphasized the significance of the variability of Pseudomonas syringae. She said INA^- Pseudomonas syringae exist in nature in numbers ranging from 10 to 80 percent of the total Pseudomonas syringae population on a given plant. Dr. Vidaver emphasized that an equilibrium exists in nature between INA^+ and INA^- Pseudomonas syringae. Dr. Vidaver said the relative ratio between INA^+ and INA^- on plants is variable depending on a number of factors, which include: the particular plant, the plant part sampled, humidity, location, temperature, and time of year. All of these factors are known to influence the distribution of INA^+ and INA^- Pseudomonas syringes.

In comparing the AGS proposal to current agricultural practices, Dr. Vidaver said large numbers of microorganisms are currently being released into the environment. She cited two example: (1) the soybean nodulating bacterium responsible for nitrogen fixation is spread as a seed inoculant all over

the U.S. every year; and (2) billions of the bacterium Bacillus thurengiensis are released to control insects such as the Japanese beetle. Dr. Vidaver said:

> "...all of these preparations, furthermore, most certainly contain a minute number of variants or mutants. The laws of probability and the principles of microbiology apply universally and these variants are to be expected. So, in these two examples mutants are released all the time."

She pointed out that since the mutants possess no selective advantage the wild-type predominates.

Dr. Vidaver said AGS proposes to field test a specific INA$^-$ mutant strain of Pseudomonas syringae. The INA$^-$ mutant strain was obtained from a parent Pseudomonas syringae INA$^+$ strain by the process of double-reciprocal recombination.

Dr. Vidaver said AGS proposes to spray less than two-tenths of an acre with 2×10^{11} colony forming units. Because 99 percent of the original inoculum is expected to die, the approximate effective concentration will be 2×10^9 viable bacteria. An elementary calculation based on simple assumptions suggests the natural population of Pseudomonas syringae in the test plot is approximately equivalent to the applied effective concentration of mutant INA$^-$ bacteria.

Dr. Vidaver said greenhouse data show the test strains are not harmful to the test plant nor are they harmful to a variety of economic plants grown in the area. Dr. Vidaver said AGS had adequately designed the test plots and proposes to monitor bacteria on test plants, on nearby plants, and in soil by a combination of tests. AGS has proposed prudent disposal methods should this be necessary.

Dr. Vidaver recommended approval of the AGS proposal with five stipulations: (1) Plants should be monitored for bacteria at shorter intervals than the proposal suggests. Sampling should be performed at the time of application and then two or three days later to obtain data on the fate of the initial inoculum. (2) Approval should be given to test a specific crop. (3) Approval should not be given for continuing tests until information has been reported to RAC showing no problems arose during the first limited field test. (4) RAC should request information on dissemination, persistence, and efficacy of the released strain. This may be done on a confidential basis. (5) Initial approval should be for one growing season. If the data reported back to RAC show no problems, RAC could recommend approval for two additional growing seasons. Dr. Vidaver said generally three growing seasons are necessary to obtain adequate predictive data in agriculture.

Dr. Vidaver said she wished to say for the record that she was more concerned with certain experiments over which RAC has no control than over the AGS proposal. Dr. Vidaver explained that one potential commercial use

of INA$^+$ bacteria is in snowmaking, to enhance the skiing season either in spring or fall. No public information is available on the strains used or the properties of these strains, nor the quantities employed in snowmaking.

Dr. Tolin concurred with Dr. Vidaver. She said the practices outlined in the AGS proposal are consistent with USDA practices, and she supported approval of the project with the five stipulations suggested by Dr. Vidaver. Dr. Fedoroff also supported Dr. Vidaver's recommendation.

Dr. Pirone said he agreed with Dr. Vidaver's analysis but requested additional information on the methodology of pathogenicity testing. Dr. Lacy also said he would like AGS to provide more information about the methods and results of pathogenicity testing. As he is familiar with Pseudomonas syringae, he did not, however, believe omission of pathogenicity testing data was critical in his evaluation of the AGS proposal. He pointed out that the proposed test site is geographically isolated from all major production areas of the test plant species. Crops grown in the vicinity of the test sites are primarily potato and alfalfa; no known isolates of Pseudomonas syringae are pathogenic to potato, alfalfa, or the test plant species.

Dr. Vidaver explained that some strains of Pseudomonas syringae are pathogenic. The majority of these pathogenic strains are considered minor pathogens, occasionally important locally but generally relatively insignificant. Dr. Vidaver said AGS in greenhouse trials tested their modified strain for pathogenicity under conditions where adverse effects to plants would have been detected. However, without field trials one cannot say unequivocally the strain would have no adverse effect on plants in the field. This is one reason field testing is necessary.

Dr. Rapp asked if AGS proposed to obtain a baseline sample of naturally occurring INA$^-$ and INA$^+$ Pseudomonas syringae before spraying their modified strain in the test field. He also asked what would be the expected recombination frequency for Pseudomonas syringae in the field. Dr. Vidaver replied AGS had not proposed to obtain a baseline sample for naturally-occurring INA$^+$ and INA$^-$ bacteria in the field before application of the modified strain.

In reply to the second of Dr. Rapp's questions, Dr. Lacy said Pseudomonas syringae pathovars under ideal laboratory conditions have a recombination frequency of 10^{-6} to 10^{-9}. In the field, however, these organisms tend to be isolated on plant surfaces in microcolonies; recombination frequency in the field would be expected to be much lower.

Dr. Lacy said he felt the AGS proposal with Dr. Vidaver's five stipulations and a requirement for additional pathogenicity data should be approved for several reasons: (1) The experiment is important; warm temperature frost damage causes hundreds of millions, if not billions of dollars loss yearly to crops in the U.S.; (2) No new genes are being introduced into the environment; (3) In this proposal, a very small portion of a genome (about

0.1%) is being modified in contrast to standard plant breeding in which 50% of a genome is modified; (4) Chemically-created INA^- have already been tested and did not cause problems; (5) This experiment is a safe "model" experiment; and (6) The NIH has already approved a similar experiment.

Dr. Pimentel said he thought the probability of environmental hazard from field testing these bacteria is minimal. Rather, he wished to use this particular proposal to help develop procedures to assess environmental impact. Dr. Pimentel said the AGS proposal describes in great detail precautions taken in the genetic engineering and culturing of the organisms; in contrast, only general statements are given concerning environmental testing. Dr. Pimentel felt more information would be needed for a good sound ecological assessment, which he felt was important as INA^+ organisms play a role in natural selection by affecting the frost tolerance of plants and insects. He made the following observation concerning environmental monitoring and the AGS proposal: (1) AGS investigators mention host range studies, but the AGS proposal contains no data on host range; (2) AGS proposes to provide a ten meter barren buffer zone surrounding the test plot but does not mention the type of vegetation surrounding the buffer zone; (3) AGS states it will sample the surrounding vegetation but does not describe sampling procedures; (4) AGS states the test organisms will be sprayed during calm night time conditions but does not describe the spraying method; and (5) AGS does not state how the test organism will be monitored for wind or insect dispersal from the test plot to surrounding areas.

Dr. Scandalios said Pseudomonas syringae is abundant in nature. He felt AGS has taken all necessary precautions, and he suggested that RAC recommend approval of the proposal with Dr. Vidaver's five stipulations.

Dr. Sharples said the proposed experiments are not threatening. She said the test organisms occur naturally in the environment. The ice nucleating gene is apparently present in a single copy per genome in INA^+ organisms and has been deleted from the test organism. This is substantially different from adding a new gene to an organism. As there is evidence that frost injury predisposes and may even be necessary for pathogenicity, INA^- strains should be less pathogenic than INA^+ strains. Dr. Sharples agreed that the AGS proposal did not adequately describe environmental monitoring, but she did not think this consideration in this instance important enough to deny AGS approval to proceed with the experiment.

Dr. Gottesman suggested RAC remember the scale of the proposal; approval is being asked for a very limited set of field tests. Approval of these field tests does not extend to commercial use. She felt many of the environmental testing questions mentioned by Dr. Pimentel are relevant to large-scale commercialization. She suggested this limited field test be permitted and pertinent data be collected.

Dr. Gottesman felt it extremely important that a distinction be drawn between trivial and non-trivial cases. She thought RAC should develop a list of

pertinent review considerations, but she did not think every question has to be asked for every experiment. Dr. Gottesman thought the experiment proposed by AGS was a "trivial case" as similar bacteria are present in nature in large numbers, and the scale of the AGS release is very small.

Dr. Pimentel said he did not believe this field test of the organism is going to cause environmental effects. However, as an ecologist, he is influenced by his knowledge of the problems caused by introductions of novel organisms. He said half the pests in the U.S. are introduced organisms. He reminded the RAC that a minor genetic change can cause some avirulent organisms to become virulent. Dr. Pimentel emphasized that introducing a reproducing organism into the environment differs from releasing a chemical. He argued that for the sake of credibility if testing is going to be done it must be done in a good sound scientific manner.

Dr. Friedman said for the sake of credibility the scientific basis of the experiment must also be taken into account. He said the AGS mutant is no different from mutants occurring in populations of these organisms in nature. Simply because the organism is created by recombinant DNA technology does not magically make it any different from naturally occurring mutants.

Dr. Pirone said he did not regard the AGS mutant any differently than he regarded naturally occurring mutants. However, the AGS strain is a deletion mutant and as the genes regulating pathogenicity are not known, it is not known whether the deletion might affect the expression of pathogenicity. He said he did not wish to see a whole range of other characteristics tested; but given that some Pseudomonas syringae isolates are pathogenic, it is prudent to test for pathogenicity. Dr. Pirone thought a prudent individual would test mutants created by whatever means for pathogenicity before field testing.

Dr. Pimentel said he supported Dr. Pirone's comments. He reiterated that he did not see a problem with field testing the AGS mutant, but he said AGS provided no data to support the phrase "no observable effects" used in describing the results of tests performed with chemically induced mutants. Walking through test plots and seeing no observable effects is not sufficient. Dr. Pimentel said anyone walking into his test plots at Cornell University where experiments are being performed with pesticides and toxic chemicals will observe no effects just by eyeing the plots. However, if the insects, arthropods, microbes, etc., are examined, tremendous differences are noted. Dr. Pimentel reiterated his statement that any environmental testing should be performed in a sound manner.

Dr. McKinney said the AGS proposal offers an opportunity to acquire some important data with little risk. While it may not be possible or feasible to do every test Dr. Pimentel suggests, RAC should take advantage of every opportunity to acquire such environmental information.

Dr. Holmes agreed with Dr. McKinney but expressed some skepticism about using the AGS experiment as a risk assessment study as it was not designed to be one.

Dr. Miller said FDA's philosophy is the amount of testing and oversight required should be that which is necessary and sufficient. He thought some of Dr. Pimentel's suggestions represent a kind of "academic feeding frenzy" of things that are intellectually desirable but wholly unnecessary in this case. Dr. Miller felt it "unreasonable to penalize AGS by requiring them to do a risk assessment study for academic reasons in a situation virtually everyone believes is extraordinarily benign."

Dr. Morris Levin of EPA said he did not feel the AGS proposal was dangerous. He asked Dr. Vidaver whether she had reservations which caused her to suggest five stipulations be attached to the approval. Dr. Vidaver replied she herself had no reservations; her five stipulations were offered to meet the concerns of several members of the assembly. The five stipulations are in keeping with the conservative manner in which RAC has operated.

Dr. Lacy felt a stepwise procedure, i.e., from a very small release to larger releases would be the way to proceed in establishing guidelines for planned releases into the environment.

Mr. Rifkin said he wanted to raise two levels of issues concerning the AGS proposal: (1) scientific questions about the AGS experiments; and (2) whether these experiments should be postponed.

Mr. Rifkin said RAC spends a lot of time on toxicity and pathogenicity, but something can be destructive in the environment without being pathogenic. He said the questions that need to be raised in terms of data on this proposal are not about pathogenicity but whether introducing INA^- in some way potentially harms balanced relationships. INA^- bacteria exist in nature, but over millions of years they existed in a certain relationship to the INA^+ in a way that maintains a balance between INA^- and INA^+ and the rest of the ecosystem. When INA^- is concentrated through a procedure of placing it on crops, that balanced relationship is changed in the small area. If it is put over millions of acres of crops and is commercially viable, the relationships in those areas will be changed.

Mr. Rifkin said the bacterium appears to promote and enhance the viability of frost-resistant plants and insects in the temperate regions of the world. He noted that many of the crops introduced in North America as cash crops were tropical in origin like tobacco and beans and corn; these crops are frost-sensitive not frost-resistant. He argued that introduced INA^- bacteria would be enhancive to tropical insects and tropical plants that are frost-sensitive, but deleterious to the natural flora and fauna that INA^+ has enhanced over a period of time, i.e., frost-resistant plants and insects.

Mr. Rifkin asked whether there were data to suggest that INA$^-$ can develop a niche. Are there any data to suggest that once INA$^-$ develops a niche it might be able to compete effectively with the INA$^+$ in the surrounding environment? Are there any data to suggest what the observable effects would be to insect life? Mr. Rifkin said we know INA$^+$ intimately affects insects.

Mr. Rifkin said:

> "I'm afraid we're using petrochemical thinking to look at biological products. With a petrochemical it makes damned good sense to talk about how much chemical you're putting out and how big the environment is that you're placing it in. When you're dealing with a biological product, quantity is not as important all the time as quality, because biological products reproduce, they migrate, they grow, you cannot put them back in the drum and take them back to the laboratory."

Mr. Rifkin said his second set of issues deal with the recent preliminary injunction stopping NIH from approving deliberate release experiments from NIH funded institutions, and whether now two standards will exist: one standard for the university community and another for industry. If the court decision is upheld, NIH may have to prepare environmental impact statements or environmental assessments under the National Environmental Policy Act (NEPA) before being allowed to approve deliberate release experiments submitted by universities.

Mr. Rifkin suggested that:

> "...the desirability of a consistent policy and program, as well as the fundamental concepts of simple fairness, require that all deliberate release experiments, or each appropriate subclass, be treated in the same manner."

Mr. Rifkin felt that:

> "...it would be entirely inappropriate for a particular deliberate release experiment submitted by a private company not to be held to the standards of environmental scrutiny...applicable to a similar experiment submitted by an NIH-funded entity."

In response to Mr. Rifkin's comments, Mr. Mitchell said the court's decision clearly stated that the preliminary injunction applied only to institutions which receive NIH funds for recombinant DNA research and specifically did not apply to voluntary submissions from industry. Mr. Mitchell pointed out that RAC is advisory in nature; the NIH Director will determine final action. He also pointed out that RAC proceeds on a case-by-case basis and reviews all proposals on their merits under a common standard.

Mr. Harvey Price of the Industrial Biotechnology Association (IBA) said:

"Since its enactment in 1969, those most familiar with NEPA's operation give it rather mixed reviews. On the one hand, it's clearly proven beneficial in many instances. In many other instances it's led directly to overly elaborate procedures accompanied by, as we may see in this case, seemingly endless and unproductive litigation. As a result, many major products have been delayed or impeded unreasonably with little or no apparent benefit to environmental protection as a final result....

"Two of the major strengths of the NIH RAC review system for recombinant DNA experiments have been the flexibility and case-by-case approach demonstrated here today, characteristics that are well-suited to the present combination of both increasing knowledge and existing uncertainty in biotechnology's nascent stage of development. This approach has been the cornerstone of NIH's commendable contribution to recombinant DNA research and hence to the biomedical and other societal benefits which are within our reach. It shouldn't be abandoned lightly....

"While it's clear that NIH will have to comply with NEPA if the Federal Courts decide, it's quite clear that it should also resist the temptation to apply that statute's often strangling formalities to areas where it is not legally applicable. Otherwise, in my view, it would be neither wise science nor wise public policy."

Mr. Rifkin said if NIH does not have regulatory power over industry, it should stop reviewing such proposals. "Voluntary compliance doesn't make sense."

X. CLOSED SESSION

The RAC went into closed session to consider proposals from commercial concerns for field testing of recombinant DNA containing organisms.

XI. ADJOURNMENT

The meeting adjourned at 5:25 p.m., Friday, June 1, 1984.

Respectively submitted,

Elizabeth A. Milewski, Ph.D.
Rapporteur

William J. Gartland, Jr., Ph.D.
Executive Secretary

I hereby certify that, to the best of my knowledge, the foregoing Minutes and Attachments are accurate and complete.

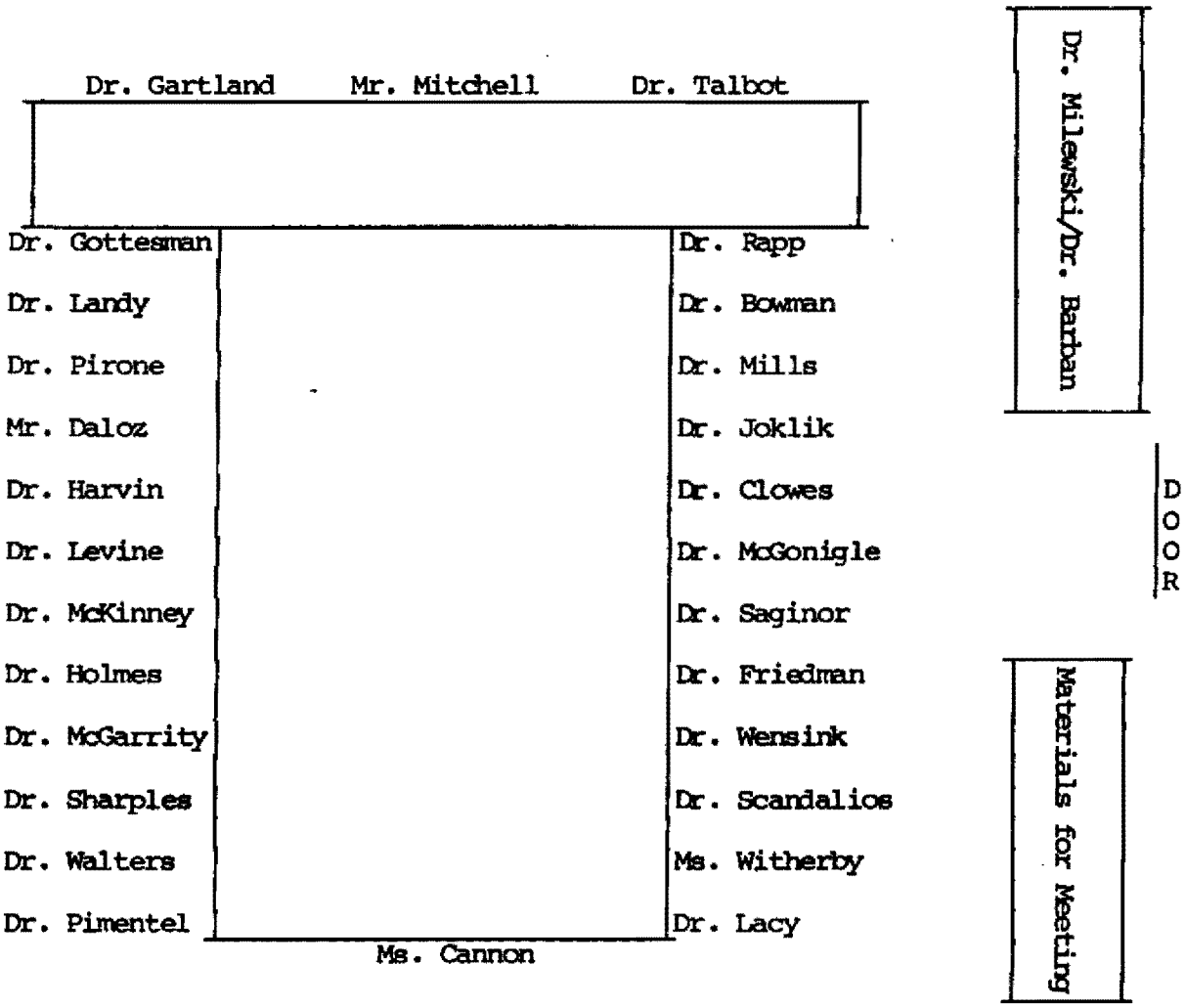
Date

Robert E. Mitchell
Chair
Recombinant DNA Advisory Committee

DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
RECOMBINANT DNA ADVISORY COMMITTEE

Building 31C, Conference Room 10
Bethesda, Maryland

October 29, 1984



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federal register

Thursday
September 20, 1984

Part III

Department of Health and Human Services

National Institutes of Health

Recombinant DNA Advisory Committee; Meeting

Recombinant DNA Research; Notice of Proposed Actions Under Guidelines

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Recombinant DNA Advisory Committee; Meeting

Pursuant to Pub. L. 92–463, notice is hereby given of a meeting of the Recombinant DNA Advisory Committee at the National Institutes of Health, Building 31C, Conference Room 10, 9000 Rockville Pike, Bethesda, Maryland 20205, on October 29, 1984, from 9:00 a.m. to adjournment at approximately 5:00 p.m. This meeting will be open to the public to discuss:

Report of the Working Group on Release into the Environment;

Report of the Working Group on Human Gene Therapy;

Amendment of Guidelines; and

Other matters to be considered by the Committee.

Attendance by the public will be limited to space available. Members of the public wishing to speak at the meeting may be given such opportunity at the discretion of the chair.

Dr. William J. Gartland, Jr., Executive Secretary, Recombinant DNA Advisory Committee, National Institutes of Health, Building 31, Room 3B10, telephone (301) 496–6051, will provide materials to be discussed at the meeting, rosters of committee members, and substantive program information. A summary of the meeting will be available at a later date.

OMB's "Mandatory Information Requirements for Federal Assistance Program Announcements" (45 FR 39592) requires a statement concerning the official government programs contained in the *Catalog of Federal Domestic Assistance*. Normally NIH lists in its announcements the number and title of affected individual programs forthe guidance of the public. Because the guidance in this notice covers not only virtually every NIH program but also essentially every federal research program in which DNA recombinant molecule techniques could be used, it has been determined to be not cost effective or in the public interest to attempt to list these programs. Such a list would likely require several additional pages. In addition, NIH could not be certain that every federal program would be included as many federal agencies, as well as private organizations, both national and international, have elected to follow the NIH Guidelines. In lieu of the individual program listing, NIH invites readers to direct questions to the information address above about whether individual programs listed in the *Catalog of Federal Domestic Assistance* are affected.

Dated: September 12, 1984.

Betty J. Beveridge,

Committee Management Officer, NIH.

[FR Doc. 84-24804 Filed 9-19-84; 8:45 am]

BILLING CODE 4140-01-M

Recombinant DNA Research; Proposed Actions Under Guidelines

AGENCY: National Institutes of Health, PHS, DHHS.

ACTION: Notice of Proposed Actions Under NIH Guidelines for Research Involving Recombinant DNA Molecules.

SUMMARY: This notice sets forth proposed actions to be taken under the NIH Guidelines for Research Involving Recombinant DNA Molecules. Interested parties are invited to submit comments concerning these proposals. After consideration of these proposals and comments by the NIH Recombinant DNA Advisory Committee (RAC) at its meeting on October 29, 1984, the Director of the National Institutes of Health will issue decisions on these proposals in accord with the Guidelines.

DATE: Comments must be received by October 22, 1984.

ADDRESS: Written comments and recommendations should be submitted to the Director, Office of Recombinant DNA Activities, Building 31, Room 3B10, National Institutes of Health, Bethesda, Maryland 20205. All comments received in timely response to this notice will be considered and will be available for public inspection in the above office on weekdays between the hours of 8:30 a.m. and 5:00 p.m. Comments received by close of business October 24, 1984, will be reproduced and distributed to the RAC for consideration at its October 29, 1984, meeting.

FOR FURTHER INFORMATION CONTACT: Background documentation and additional information can be obtained from Drs. Stanley Barban and Elizabeth Milewski, Office of Recombinant DNA Activities, National Institutes of Health, Bethesda, Maryland 20205, (301) 496–6051.

SUPPLEMENTARY INFORMATION: The National Institutes of Health will consider the following actions under the Guidelines for Research Involving Recombinant DNA Molecules.

I. Proposed Amendment of Section III–D of the Guidelines.

In a letter dated August 21, 1984, Mr. C. Searle Wadley and Dr. John H. Keene of Abbott Laboratories, North Chicago, Illinois, propose that the following sentence be added to Section III–D of the Guidelines:

Although these experiments are exempt, it is recommended that they be performed at the appropriate biosafety level for the host or recombinant organism (for biosafety levels see "Biosafety in Microbiological and Biomedical Laboratories").

In support of their proposal, Mr. Wadley and Dr. Keene state that it would be advisable to recommend that appropriate biosafety levels be considered for those recombinant experiments that are exempt from the Guidelines.

II. Proposed Addition of Prohibited Experiments to the Guidelines.

Mr. Jeremy Rifkin of the Foundation on Economic Trends, Washington, D.C., submitted the following letter, dated August 21, 1984, to NIH:

I am formally requesting that the following item be placed on the agenda for the October 29, 1984 meeting of the Recombinant DNA Advisory Committee of the National Institutes of Health.

It has come to our attention that the National Institutes of Health and the National Science Foundation are helping to fund specific experiments by Dr. Ralph Brinster of the University of Pennsylvania in which human genes regulating growth hormone is being injected in to sheep and pig embryos with the express purpose of incorporating these human genes permanently into the germ line of these other mammalian species. These experiments are currently being conducted, in part, with the assistance and cooperation of the USDA at its agricultural experimental station at Beltsville, Maryland.

If successful, these experiments would represent the second time in history that a segment of the genetic make-up of homo-sapiens has been permanently transferred into the genetic make-up of another species. The Brinster team has already successfully transferred the human growth hormone gene into the germ line of mice. Thus, a dramatic new technological threshold has been crossed, making it imperative that the Federal Government act immediately and expeditiously to establish a policy in regard to such experimentation.

Therefore, I am proposing the following amendment to the NIH guidelines for recombinant DNA experimentation:

The NIH prohibits any experimentation involving the transfer of a genetic trait from one mammalian species into the germ line of another unrelated mammalian species. "Unrelated" shall be defined as any two species that cannot mate and produce one generation of offspring either in the wild or under pre-existing domestic breeding programs.

This NIH guideline shall encompass all mammalian species, including homo-sapiens. Upon adoption of this guideline by the NIH, said agency shall immediately discontinue funding any current experimental research involving the transfer of genetic traits from one mammalian species into the germ line of another unrelated mammalian species and shall instruct all institutions receiving NIH

grants that any such experimentation using private funds shall be grounds for the immediate suspension of all NIH research grants to the institution. This amendment shall also cover all private companies who are signatories of license agreements with NIH funded institutions where said agreements contain clauses requiring the licensee to adhere to the NIH guidelines involving recombinant DNA experimentation.

The intent of this amendment to the NIH guidelines is to protect the biological integrity of every mammalian species. Existing Federal policy, as reflected in many Federal statutes, protects the integrity and well being of species. The crossing of species borders and the incorporation of genetic traits from one species directly into the germ line of another species represents a fundamental assault on the principle of species integrity and violates the right of every species to exist as a separate, identifiable creature.

Certainly most human beings would condemn any attempt to introduce animal genes permanently into the germ line of homo-sapiens. We would abhor any such experiment as a gross and unconscionable violation of our telos as a species. In like manner this amendment establishes the principle that similar experiments between all other mammalian species be condemned and outlawed on the same grounds, i.e., that such an intrusion violates the telos of each species and is to be condemned as morally reprehensible.

As to non-mammalian species, the same principle of species integrity ought to apply. Therefore, I am proposing that in addition to the adoption of the above amendment to the NIH guidelines, the RAC immediately establish a working sub-group whose purpose will be to propose any additional protocols or guidelines that might be necessary to ensure compliance with the spirit of the above amendment in regard to the protection of the gem line of all species.

On August 23, 1984, Mr. Rifkin submitted an additional letter to NIH:

I am submitting an additional item for placement on the agenda for the October 29, 1984 meeting of the Recombinant DNA Advisory Committee of the National Institutes of Health. The following amendment to the NIH guidelines should be raised for discussion and debate along with the proposed amendment which I forwarded to you in my letter dated August 21, 1984. I would like this enclosed amendment to be considered first on the agenda and the amendment in my August 21 letter to be considered second.

The amendment shall read as follows:

The National Institutes of Health prohibits any experimentation involving the transfer of a genetic trait from a human being into the germ line of another mammalian species. The National Institutes of Health also prohibits any experimentation involving the transfer of a genetic trait from any mammalian species into the germ line of a human being. Furthermore, the National Institutes of Health considers any such experimentation involving the transfer of genetic traits between animal and human germ lines to be morally and ethically unacceptable.

Thank you for your time and consideration on this matter.

OMB's "Mandatory Information Requirements for Federal Assistance Program Announcements" (45 FR 39592) requires a statement concerning the offical government programs contained in the *Catalog of Federal Domestic Assistance*. Normally NIH lists in its announcements the number and title of affected individual programs for the guidance of the public. Because the guidance in this notice covers not only virtually every NIH program but also essentially every federal research program in which DNA recombinant molecule techniques could be used, it has been determined to be not cost effective or in the public interest to attempt to list these programs. Such a list would likely require several additional pages. In addition, NIH could not be certain that every federal program would be included as many federal agencies, as well as private organizations, both national and international, have elected to follow the NIH Guidelines. In lieu of the individual program listing, NIH invites readers to direct questions to the information address above about whether individual programs listed in the *Catalog of Federal Domestic Assistance* are affected.

Dated: September 10, 1984.

Bernard Talbot, M.D., Ph.D.,

Acting Director, National Institute of Allergy and Infectious Diseases, National Institutes of Health.

[FR Doc. 84-24912 Filed 9-19-84; 8:45 am]

BILLING CODE 4140-01-M

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DEPARTMENT OF PEDIATRICS

UCLA SCHOOL OF MEDICINE
HARBOR-UCLA MEDICAL CENTER
1000 WEST CARSON STREET
TORRANCE, CALIFORNIA 90509

1195

October 22, 1984

Dr. William J. Gartland
Executive Secretary, RAC
National Institute of Allergy
and Infectious Diseases
Building 31, 3B-10
Bethesda, MD 20205

Dear Dr. Gartland:

We write in response to a communication from Mr. Jeremy Rifkin to the RAC requesting that all transgenic experiments between species be terminated in order to protect species purity. Our letter restricts itself to the impact of this request on human genetic experimentation and potential therapy. We shall not address ourselves to the propositions of species integrity, since as we shall point out below, this issue has no practical relevance to human genetic investigations.

Transgenic experiments between species are especially important to the advancement of human genetic knowledge -- basic and applied. Our direct understanding of mechanisms of gene function and regulation depends on the isolation, modification, and functional evaluation of cloned genes. This kind of experiment can be best accomplished by the transfer of human genes into laboratory mice. The transfer of human genes into human embryos for experimental purposes is obviated on account of moral, ethical, and practical considerations. The mouse provides an acceptable alternative, providing as it does, a means of evaluating genetic expression in all cell types at all stages of development in a reproducible manner. The transfer of human genes into laboratory mice cannot be considered as modifying the genetics of the murine species, since only laboratory mice will be used, and these animals will either be confined to the laboratory or killed at the end of an experiment.

In addition to obtaining basic information on the functioning of human genes, transgenic experiments will provide the most effective way of testing modified human genes for the purpose of somatic cell genetic therapy. Many laboratories are currently attempting to ameliorate certain human genetic diseases by means of the transfer of human genes into the body cells of patients. It is generally believed that serious genetic diseases such as sickle cell disease, and various thalassemias can be treated in this way. The prohibition of interspecific transgenic experiments would likely slow down or abort the development of these new therapies.

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In summation, we believe Mr. Rifkin's recommendations make little sense in the context of present day human medical genetics. The transgenic system provides a unique means by which fundamental knowledge of human gene expression and regulation can be acquired. Such information will be invaluable in the future for the development of diagnostic tests and therapeutic regimens for a host of human disease conditions. The information can also be expected to be crucial in the design of disease prevention strategies. The transgenic system also provides the best means by which candidate genes for human genetic therapy can be adequately tested. It is also clear that these objectives can be realized without any threat to the short or long term genetic constitution or function of species.

Sincerely,

David L. Rimoin, M.D., Ph.D.
President, American Society of Human Genetics

Frank H. Ruddle, Ph.D., President-Elect
Kenneth K. Kidd, Ph.D.
C. Thomas Caskey, M.D.
Larry J. Shapiro, M.D.

DLR/dr

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

OCT 2 4 1984

Dr. William Gartland
Office of Recombinant DNA Activities
National Institute for Allergy
and Infectious Disease
National Institutes of Health
Bethesda, MD 20205

Dear Dr. Gartland:

As you know, the Assistant Secretary for Health recently convened a group within the PHS, the Ad Hoc Committee on Biotechnology, to serve as a focal point for PHS deliberations on issues regarding biotechnology. On behalf of that committee, we wish to offer comments on two proposals to amend the NIH Guidelines on Recombinant DNA Research. These proposals by the Foundation on Economic Trends are described in documents designated 1182 and 1183.

The proposed amendments to the Guidelines would, in essence, prohibit the inter-species transfer of "genetic traits" between mammals. In our opinion, such prohibitions are not warranted by the canons of science, and could inflict incalculable damage on several areas of scientific and medical inquiry (vide infra). Hence, we urge that the proposed amendments be rejected. These views are explicated below.

First, terms such as "genetic trait" are so vague as to be meaningless in the context of transfer of individual genes, which are, of course, merely homopolymers of nucleic acid. It is not unusual for experiments to employ genes that are hybrids, with regulatory and structural sequences derived from different sources, perhaps even including chemically-synthesized regions that do not occur in nature. Moreover, the transfer of single genes does not confer species identity - or the loss thereof - on an organism.

Second, the proposed prohibitions would inhibit the study of the role of specific genes in susceptibility to disease. For example, the recent experiments of Professor Philip Leder with transgenic mice that have begun to elucidate the nature of genetic susceptibility to breast cancer would be proscribed.

Third, the proposed prohibitions would confound the new vistas that recombinant DNA technology provides for developmental biology. The insertion of controllable heterologous genes whose activity is manipulable into embryos will provide important insights into the role of various genes in development.

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Fourth, the proposals ignore the well-established practice of inter-species applications of single-gene polypeptide products, arguably analogous to transfer of the gene itself. These applications include, for example, the administration to human patients of bovine and porcine insulin and salmon calcitonin. Note also that human patients have long been the recipient of porcine cardiac valves, and of complex secondary metabolites of microbes, e.g., antibiotics. In addition, the use of various analogues of naturally-occurring molecules, such as fertility and growth hormones and lymphokines, has established the use of "gene products" that do not exist in any species in nature.

Fifth, the proposed prohibitions would prevent optimal pre-clinical testing of the products and procedures intended for clinical trials of human gene therapy. The outcome would be that these clinical trials would be more hazardous, less likely to succeed, and, inevitably, delayed. This would represent certain detriment to patients afflicted with genetic disorders amenable to gene therapy.

In summary, we urge the RAC to consider seriously the above objections to the proposals submitted by the Foundation on Economic Trends, and to reject those proposals.

Sincerely yours,

Dr. Frank Young, Chair
Food and Drug Administration

Dr. Gary Noble
Centers for Disease Control

Dr. Peter Bridge
Alcohol, Drug Abuse and Mental Health Administration

Dr. Audrey Manley
Health Resources and Services Administration

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THE JOHNS HOPKINS UNIVERSITY
SCHOOL OF MEDICINE
and
THE JOHNS HOPKINS HOSPITAL

DEPARTMENT OF PEDIATRICS
Developmental Genetics Laboratory

Mailing Address:
Room 6-124
The Children's Medical & Surgical Center
THE JOHNS HOPKINS HOSPITAL
Baltimore, Md. 21205
Tel: (301) 955-6621

October 24, 1984

Director
Office of Recombinant DNA Activities
Building 31 Room 3B10
National Institutes of Health
Bethesda, MD 20205

Re: Proposed Addition of Prohibited Experiments to the Guidelines, submitted by Mr. Jeremy Rifkin of the Foundation on Economic Trends, dated August 21, 1984 and August 23, 1984.

Dear Director:

We are concerned about the scientific merit of the recent prohibitions of transfers of genetic traits proposed by Mr. Rifkin. Aside from the tremendous benefits to be accrued by humans by utilizing gene transfer systems (such as the manufacturing of insulin by bacteria, and the production of disease resistant plants and animals), Mr. Rifkin's basic premise is not a biological argument. The intent of this amendment is to protect the biological integrity of every mammalian species, yet the concept of retaining species integrity is contrary to evolutionary thought.

Species are man-made classifications that designate life forms of like individuals, based primarily on morphology. Evolution does not act on species, but upon individuals within a species. Each individual contributing to the gene pool of a species is genetically different and unique. The gene pool of a given species is not stagnant, it changes constantly albeit at a slow rate. We all recognize the importance of maintaining the gene pool. The introduction of genetic material into individuals does not destroy the gene pool of a given species.

Utilizing classical, Mendelian genetics, we have manipulated the genes of literally thousands of individuals (both plant and animals) to provide domesticated varieties, etc., of many food sources and for many lifeforms that we deem attractive and desirable. How does this differ from introducing genes into individuals of a species? We are not destroying the gene pool, just utilizing some of the individuals to create homogeneous varieties, breeds, etc.

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There exist natural vectors that exchange DNA between species, the viruses. Lewis Thomas in his book, The Lives of a Cell (1974), addresses this issue of viruses as mobile genes dragging along pieces of genome and current research unequivocally demonstrates this point. The only difference between this natural mixing of genomes and the introduction of specific genes is that the latter is more directed.

We feel that the proposed amendment lacks scientific validity and therefore should not be approved.

Sincerely yours,

John Gearhart

John Gearhart, Ph.D.
Associate Professor of Pediatrics, Gynecology and Obstetrics, Cell Biology and Anatomy
Joseph P. Kennedy, Jr. Scholar in Mental Retardation

Mary Lou Oster-Granite

Mary Lou Oster-Granite, Ph.D.
Associate Professor of Pediatrics and Neuroscience

JG;MLOG/pb

The University of Texas Medical Branch at Galveston

Medical School
Graduate School of Biomedical Sciences
School of Allied Health Sciences
School of Nursing

Marine Biomedical Institute
Institute for the Medical Humanities
UTMB Hospitals at Galveston

DEPARTMENT OF HUMAN BIOLOGICAL CHEMISTRY & GENETICS
Office of the Chairman

Area Code 409
761-2271

October 23, 1984

FOR CONSIDERATION AT October 29, 1984 Meeting, please.

Director
Office of Recombinant DNA Activities
Building 31, Room 3B10
National Institutes of Health
Bethesda, MD. 20205

Dear Director:

This is in comment to the proposed addition of prohibited experiments to the guidelines suggested by Mr. Jeremy Rifkin of the Foundation on Economic Trends and included in the Federal Register, Volume 49, No. 184, Thursday, September 20, 1984. Mr. Rifkin suggests prohibiting all experiments which involve the transfer of a genetic trait from one mammalian species into the germ line of another unrelated mammalian species. He attempted to justify this suggestion by a series of assertions which have no basis in fact or in any other reason than his own opinion. Thus he claims that such experiments represent, "fundamental assault on the principle of species integrity." He asserts that every species has a right to exist as a separate, identifiable creature, etc., etc. Certainly Mr. Rifkin is entitled to his opinions. He is not entitled to make them natural laws simply by assertion. In fact, his assertions are uniformly wrong. The truth is that man has been experimenting with crossing animal species since time immemorial. The technology available to do it now simply differs from that available formerly. It is, in my opinion, dangerous and wrong for a prohibition of the sort suggested to be put into place as part of the framework in which American research is conducted. It would undoubtedly deter important and potentially useful experiments from being done, experiments which would have potential for improving the lot of many species including but not limited to mankind.

Sincerely yours,

E. Brad Thompson, M.D.
Chairman and Professor

EBT:sg

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SCHOOL OF MEDICINE
DEPARTMENT OF BIOCHEMISTRY AND BIOPHYSICS

SAN FRANCISCO, CALIFORNIA 94143
(415) 666-4324

October 23, 1984

Dr. William J. Gartland
Executive Secretary, RAC
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, Maryland 20205

Dear Dr. Gartland,

I am writing to express my strong concern over the amendments proposed by Mr. Jeremy Rifkin, which were published in the Federal Register (volume 49:37016-37017, which I received today), for discussion at the RAC meeting to take place October 29, 1984. I was informed in a phone conversation with the RAC office today that it would be possible to have these comments accepted so long as they arrived by October 26th.

Although I am presently the Vice-President of the Genetics Society of America as well as President-elect (for 1985), I am presenting my comments not in any official capacity for the Society but rather as a concerned--deeply concerned--geneticist.

Mr. Rifkin's amendment of August 23, 1984 proposes a prohibition of transfer of a genetic trait (i) from a human being into the germ line of another mammalian species and (ii) from any mammalian species into the germ line of a human being. I am opposed to a blanket prohibition of these two types of procedures in large part because I believe that such procedures will yield information that will have important, beneficial consequences for the health and well being of both humans and other mammals. My specific reasons follow.

DNA transfer from humans or other mammals into non-human mammals makes it possible to address fundamental questions in developmental biology concerned with gene expression. In addition such transfer experiments make it possible to address fundamental questions concerned with carcinogenesis. Information gleaned from these experiments is certain to provide important new insights into disease processes both in humans and in other mammals. The end result will be a literal strengthening of species, a deeper understanding that will improve the ability of these species to combat disease.

Without hearing the report of the Working Group on Human Gene Therapy that is to be presented at the October 29 meeting, I am hesitant to take a firm position on the transfer of traits from a human or non-human mammal into the human germ line. Obviously, this procedure must be considered within the context of guidelines governing experimentation involving human subjects. With these disclaimers aside, my present personal feeling is that

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I do not think that such transfers should be done. Despite this feeling, I do not believe that the National Institutes of Health should make a permanent prohibition against such procedures. It is possible that judicious use of this procedure might be called for in certain circumstances or shall result in important and unique information. I feel that such a procedure should be utilized only after rigorous scrutiny by appropriate oversight committees or panels.

In Mr. Rifkin's letter of August 21, 1984, he proposes further that "the same principle of species integrity ought to apply ... to non-mammalian species" (page 37017). In other words, Mr. Rifkin proposes that the National Institutes of Health prohibit transfer of genetic traits, for example, from mammals and other organisms into bacteria and yeast. Such a prohibition would have disasterous consequences on many levels. First, it would stop dead in its tracks the greatest revolution in understanding of the natural world that has ever taken place: the technique of cloning (that is, isolating) individual genes from complex organisms is providing a flood of information and insights that is unprecedented. Secondly, the practical consequences of these types of genetic transfers for production of biological products and reagents are immense. The technique of genetic trait transfer is an essential cornerstone in both of these broad areas. With respect to the latter, the United States is without question the world leader in development and utilization of biotechnology. It is crucial to maintain and sustain this critical technology and to nurture it wisely. In the same spirit, it is fundamental discoveries from basic science that launched the biotechnology industry and that fuel its continued progress. Prohibition of these types of genetic trait transfers would cripple modern bio-medical science and biotechnology.

Sincerely yours,

Ira Herskowitz

Dr. Ira Herskowitz
Professor and Vice-Chairman,
Department of Biochemistry & Biophysics
Head, Division of Genetics

511

October 16, 1984

Route #7, Box 487
Athens, Ohio 45701

Director
Office of Recombinant DNA Activities
Building 31, Room 3B10
National Institute of Health
Bethesda, Md. 20205

Dear Director:

It is imperative that the research now going on in Recombinant DNA not be stopped or delayed. As parents with two daughters afflicted with Metachromatic Leukodystrophy, we are only to aware of the possible consequences of any interruption in this work.

The existence of the Recombinant DNA Advisory Committee points to the fact that the National Institute of Health is responsibly overseeing the research in this field. To adopt Mr. Rifkin amendments would destroy Recombinant DNA research and with it the hope of treatment for our daughters and thousand of other patients and families of patients suffering from many currently untreatable diseases.

We believe in this technology and have donated funds to provide a research technician in the lab of Dr. John O'Brian of the University of California at San Diego. This person is to assist Dr. O'Brian in the cloning of the Aryl Sulphatase A gene which does not properly function in MLD patients.

We know we have a long road to travel, but feel we are headed in the right direction. Please continue this important work.

Very truly yours,

J Michael Downard

J. Michael Downard

Christina L Downard

Christina L. Downard

512

P. O. Box 264
New Marshfield, Ohio 45766
October 17, 1984

Director
Office of Recombinant DNA Activities
Building 31, Room 3B10
National Institutes of Health
Bethesda, Maryland 20205

Dear Director:

I am writing in reference to a proposal by Mr. Jeremy Rifkin regarding recombinant DNA research. I urge you NOT to consider this amendment. I have two granddaughters suffering with Metachromatic Leukodystrophy. At this time, our only hope for a cure for these girls is with recombinant DNA research. We cannot afford even the shortest delay. Research must continue!

This research could give these two beautiful little girls a chance for a cure and a normal life. Please do not deprive our family and other families of this hope of happiness.

Sincerely,

E. Eileen Saylor

E. Eileen Saylor

513

October 5, 1984

Director, Office of Recombinant DNA Activities
Building 31, Room 3B10
National Institutes of Health
Bethesda, MD 20205

Dear Director:

I am writing in response to Mr. Jeremy Rifkin's proposed amendment to the National Institute of Health's Guidelines for Research involving Recombinant DNA Molecules as outlined in the September 20, 1984 Federal Register.

I am very concerned that Mr. Rifkin's proposal does not take into consideration the discontinuance of important medical research relative to genetic disorders, cancer and other diseases. I am specifically interested in the continuation of this research as it relates to a rare genetic disease known as Metachromatic Leukodystrophy. I am familiar with the Downard family in Athens, Ohio who have two young children with this particular disease. It is my understanding that this research is currently the most viable possibility for cure or treatment for these two and many other children suffering from genetic diseases.

I strongly urge the committee not to adopt the proposed amendment and instead continue the funding for Recombinant DNA Activities Research.

Sincerely,

Christopher R. Wilson

Rockbridge, OH

5 14

October 5, 1984

Director, Office of Recombinant DNA Activities
Building 31, Room 3B10
National Institutes of Health
Bethesda, MD 20205

Dear Director:

I am writing in response to Mr. Jeremy Rifkin's proposed amendment to the National Institute of Health's Guidelines for Research involving Recombinant DNA Molecules as outlined in the September 20, 1984 Federal Register.

I am very concerned that Mr. Rifkin's proposal does not take into consideration the discontinuance of important medical research relative to genetic disorders, cancer and other diseases. I am specifically interested in the continuation of this research as it relates to a rare genetic disease known as Metachromatic Leukodystrophy. I am familiar with the Downard family in Athens, Ohio who have two young children with this particular disease. It is my understanding that this research is currently the most viable possibility for cure or treatment for these two and many other children suffering from genetic diseases.

I strongly urge the committee not to adopt the proposed amendment and instead continue the funding for Recombinant DNA Activities Research.

Sincerely,

Donald J. Monnette

Rockbridge, OH

515

October 5, 1984

Director, Office of Recombinant DNA Activities
Building 31, Room 3B10
National Institutes of Health
Bethesda, MD 20205

Dear Director:

I am writing in response to Mr. Jeremy Rifkin's proposed amendment to the National Institute of Health's Guidelines for Research involving Recombinant DNA Molecules as outlined in the September 20, 1984 Federal Register.

I am very concerned that Mr. Rifkin's proposal does not take into consideration the discontinuance of important medical research relative to genetic disorders, cancer and other diseases. I am specifically interested in the continuation of this research as it relates to a rare genetic disease known as Metachromatic Leukodystrophy. I am familiar with the Downard family in Athens, Ohio who have two young children with this particular disease. It is my understanding that this research is currently the most viable possibility for cure or treatment for these two and many other children suffering from genetic diseases.

I strongly urge the committee not to adopt the proposed amendment and instead continue the funding for Recombinant DNA Activities Research.

Sincerely,

Clarence E. Herring

Rockbridge, OH

516

October 5, 1984

Director, Office of Recombinant DNA Activities
Building 31, Room 3B10
National Institutes of Health
Bethesda, MD 20205

Dear Director:

I am writing in response to Mr. Jeremy Rifkin's proposed amendment to the National Institute of Health's Guidelines for Research involving Recombinant DNA Molecules as outlined in the September 20, 1984 Federal Register.

I am very concerned that Mr. Rifkin's proposal does not take into consideration the discontinuance of important medical research relative to genetic disorders, cancer and other diseases. I am specifically interested in the continuation of this research as it relates to a rare genetic disease known as Metachromatic Leukodystrophy. I am familiar with the Downard family in Athens, Ohio who have two young children with this particular disease. It is my understanding that this research is currently the most viable possibility for cure or treatment for these two and many other children suffering from genetic diseases.

I strongly urge the committee not to adopt the proposed amendment and instead continue the funding for Recombinant DNA Activities Research.

Sincerely,

Jolene Wilson

Rockbridge, OH

517

October 5, 1984

Director, Office of Recombinant DNA Activities
Building 31, Room 3B10
National Institutes of Health
Bethesda, MD 20205

Dear Director:

I am writing in response to Mr. Jeremy Rifkin's proposed amendment to the National Institute of Health's Guidelines for Research involving Recombinant DNA Molecules as outlined in the September 20, 1984 Federal Register.

I am very concerned that Mr. Rifkin's proposal does not take into consideration the discontinuance of important medical research relative to genetic disorders, cancer and other diseases. I am specifically interested in the continuation of this research as it relates to a rare genetic disease known as Metachromatic Leukodystrophy. I am familiar with the Downard family in Athens, Ohio who have two young children with this particular disease. It is my understanding that this research is currently the most viable possibility for cure or treatment for these two and many other children suffering from genetic diseases.

I strongly urge the committee not to adopt the proposed amendment and instead continue the funding for Recombinant DNA Activities Research.

Sincerely,

Christine Wilson

Rockbridge, OH

518

October 5, 1984

Director, Office of Recombinant DNA Activities
Building 31, Room 3B10
National Institutes of Health
Bethesda, MD 20205

Dear Director:

I am writing in response to Mr. Jeremy Rifkin's proposed amendment to the National Institute of Health's Guidelines for Research involving Recombinant DNA Molecules as outlined in the September 20, 1984 Federal Register.

I am very concerned that Mr. Rifkin's proposal does not take into consideration the discontinuance of important medical research relative to genetic disorders, cancer and other diseases. I am specifically interested in the continuation of this research as it relates to a rare genetic disease known as Metachromatic Leukodystrophy. I am familiar with the Downard family in Athens, Ohio who have two young children with this particular disease. It is my understanding that this research is currently the most viable possibility for cure or treatment for these two and many other children suffering from genetic diseases.

I strongly urge the committee not to adopt the proposed amendment and instead continue the funding for Recombinant DNA Activities Research.

Sincerely,

Joseph Ziegler

Rockbridge, OH

519

October 5, 1984

Director, Office of Recombinant DNA Activities
Building 31, Room 3B10
National Institutes of Health
Bethesda, MD 20205

Dear Director:

I am writing in response to Mr. Jeremy Rifkin's proposed amendment to the National Institute of Health's Guidelines for Research involving Recombinant DNA Molecules as outlined in the September 20, 1984 Federal Register.

I am very concerned that Mr. Rifkin's proposal does not take into consideration the discontinuance of important medical research relative to genetic disorders, cancer and other diseases. I am specifically interested in the continuation of this research as it relates to a rare genetic disease known as Metachromatic Leukodystrophy. I am familiar with the Downard family in Athens, Ohio who have two young children with this particular disease. It is my understanding that this research is currently the most viable possibility for cure or treatment for these two and many other children suffering from genetic diseases.

I strongly urge the committee not to adopt the proposed amendment and instead continue the funding for Recombinant DNA Activities Research.

Sincerely,

Norma Hobel

Rockbridge, OH

520

October 5, 1984

Director, Office of Recombinant DNA Activities
Building 31, Room 3B10
National Institutes of Health
Bethesda, MD 20205

Dear Director:

I am writing in response to Mr. Jeremy Rifkin's proposed amendment to the National Institute of Health's Guidelines for Research involving Recombinant DNA Molecules as outlined in the September 20, 1984 Federal Register.

I am very concerned that Mr. Rifkin's proposal does not take into consideration the discontinuance of important medical research relative to genetic disorders, cancer and other diseases. I am specifically interested in the continuation of this research as it relates to a rare genetic disease known as Metachromatic Leukodystrophy. I am familiar with the Downard family in Athens, Ohio who have two young children with this particular disease. It is my understanding that this research is currently the most viable possibility for cure or treatment for these two and many other children suffering from genetic diseases.

I strongly urge the committee not to adopt the proposed amendment and instead continue the funding for Recombinant DNA Activities Research.

Sincerely,

Greg Gedgl

Rockbridge, OH

521

October 5, 1984

Director, Office of Recombinant DNA Activities
Building 31, Room 3B10
National Institutes of Health
Bethesda, MD 20205

Dear Director:

I am writing in response to Mr. Jeremy Rifkin's proposed amendment to the National Institute of Health's Guidelines for Research involving Recombinant DNA Molecules as outlined in the September 20, 1984 Federal Register.

I am very concerned that Mr. Rifkin's proposal does not take into consideration the discontinuance of important medical research relative to genetic disorders, cancer and other diseases. I am specifically interested in the continuation of this research as it relates to a rare genetic disease known as Metachromatic Leukodystrophy. I am familiar with the Downard family in Athens, Ohio who have two young children with this particular disease. It is my understanding that this research is currently the most viable possibility for cure or treatment for these two and many other children suffering from genetic diseases.

I strongly urge the committee not to adopt the proposed amendment and instead continue the funding for Recombinant DNA Activities Research.

Sincerely,

Kenneth R. Wilson

Rockbridge, OH

522

October , 1984

Director, Office of Recombinant DNA Activities
Building 31, Room 3B10
National Institutes of Health
Bethesda, MD 20205

Dear Director:

I am writing in response to Mr. Jeremy Rifkin's proposed amendment to the National Institute of Health's Guidelines for Research involving Recombinant DNA Molecules as outlined in the September 20, 1984 Federal Register.

I am very concerned that Mr. Rifkin's proposal does not take into consideration the discontinuance of important medical research relative to genetic disorders, cancer and other diseases. I am specifically interested in the continuation of this research as it relates to a rare genetic disease known as Metachromatic Leukodystrophy. I am familiar with the Downard family in Athens, Ohio who have two young children with this particular disease. It is my understanding that this research is currently the most viable possibility for cure or treatment for these two and many other children suffering from genetic diseases.

I strongly urge the committee not to adopt the proposed amendment and instead continue the funding for Recombinant DNA Activities Research.

Sincerely,

Rory R Wilson

Rockbridge, OH

523

October 16, 1984
Director, Office of Recombinant DNA Activities
Building 31, Room 3B10
National Institute of Health
Bethesda, MD. 20205

Dear Director;

I am writing this letter in response to the proposed amendment to the National Institute of Health's Guidelines for Research involving Recombinant DNA Molecules as submitted by Mr. Jeremy Rifkin of the Foundation on Economic Trends.

Because I am concerned that Mr. Rifkin's proposal will discontinue research important to the cure of genetic disorders, including cancer, I urge the committee to overrule the proposed amendment and continue the funding of Recombinant DNA Activities Research.

Sincerely,
Tricia Stewart
Elizabethtown, KY

524

October 19, 1984

Director, Office of Recombinant DNA Activities
Building 31, Room 3B10
National Institutes of Health
Bethesda, MD 20205

Dear Director:

I am writing in response to Mr. Jeremy Rifkin's proposed amendment to the National Institute of Health's Guidelines for Research involving Recombinant DNA Molecules as outlined in the September 20, 1984 Federal Register.

I am very concerned that Mr. Rifkin's proposal does not take into consideration the discontinuance of important medical research relative to genetic disorders, cancer and other diseases. I am specifically interested in the continuation of this research as it relates to a rare genetic disease known as Metachromatic Leukodystrophy.. I am familiar with the Downard family in Athens, Ohio who have two young children with this particular disease. It is my understanding that this research is currently the most viable possibility for cure or treatment for these two and many other children suffering from genetic diseases.

I strongly urge the committee not to adopt the proposed amendment and instead continue the funding for Recombinant DNA Activities Research.

Sincerely,

Debra Walker

105 W. Lancaster St
Athens, OH 45701

525

October 19, 1984

Director, Office of Recombinant DNA Activities
Building 31, Room 3B10
National Institutes of Health
Bethesda, MD 20205

Dear Director:

This letter is in reference to a proposal by Mr. Jeremy Rifkin regarding recombinant DNA research which appeared in the Federal Register Volume 40, Number 184, September 20, 1984.

I am aware of a family with two young children suffering from a rare genetic disease known as Metachromatic Leukodystrophy. My understanding is that this is a terminal illness, and that the greatest hope for a cure lies in recombinant genetic research which would be prohibited by the Rifkin proposal. On behalf of the children I know of who are suffering, their parents, and other suffering children unknown to myself, I urge this office to strongly consider research toward a cure for this disease, as well as other important research, upon which Mr. Rifkin's proposal would have a serious impact.

Thank you for your consideration.

Yours truly,

Hilla M. Zerbst

Hilla M. Zerbst
159 Valley View Estates
Athens, OH 45701

526

October 19, 1984

Director, Office of Recombinant DNA Activities
Building 31, Room 3B10
National Institutes of Health
Bethesda, MD 20205

Dear Director:

I am writing in response to Mr. Jeremy Rifkin's proposed amendment to the National Institute of Health's Guidelines for Research involving Recombinant DNA Molecules as outlined in the September 20, 1984 Federal Register.

I am very concerned that Mr. Rifkin's proposal does not take into consideration the discontinuance of important medical research relative to genetic disorders, cancer and other diseases. I am specifically interested in the continuation of this research as it relates to a rare genetic disease known as Metachromatic Leukodystrophy. I am familiar with the Downard family in Athens, Ohio who have two young children with this particular disease. It is my understanding that this research is currently the most viable possibility for cure or treatment for these two and many other children suffering from genetic diseases.

I strongly urge the committee not to adopt the proposed amendment and instead continue the funding for Recombinant DNA Activities Research.

Sincerely,

Shirley Lemley

Athens, OH

527

October 19, 1984

Director, Office of Recombinant DNA Activities
Building 31, Room 3B10
National Institutes of Health
Bethesda, MD 20205

Dear Director:

This letter is in reference to a proposal by Mr. Jeremy Rifkin regarding recombinant DNA research which appeared in the Federal Register Volume 40, Number 184, September 20, 1984.

I am aware of a family with two young children suffering from a rare genetic disease known as Metachromatic Leukodystrophy. My understanding is that this is a terminal illness, and that the greatest hope for a cure lies in recombinant genetic research which would be prohibited by the Rifkin proposal. On behalf of the children I know of who are suffering, their parents, and other suffering children unknown to myself, I urge this office to strongly consider research toward a cure for this disease, as well as other important research, upon which Mr. Rifkin's proposal would have a serious impact.

Thank you for your consideration.

Yours truly,

Pam Walton

Athens, OH

528

RECOMBINANT DNA ADVISORY COMMITTEE

WORKING GROUP ON HUMAN GENE THERAPY

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DRAFT

POINTS TO CONSIDER IN THE DESIGN AND SUBMISSION OF HUMAN GENE THERAPY PROTOCOLS

WORKING GROUP ON HUMAN GENE THERAPY
RECOMBINANT DNA ADVISORY COMMITTEE

OUTLINE

Preamble

A. Focus on somatic-cell gene therapy

B. Guidance provided by general rules for research involving human subjects and President's Commission report on Splicing Life

C. Review procedures

D. Procedure for periodic revision of "Points to Consider"

I. Issues Covered by the Department of Health and Human Services (DHHS) Regulations for Research Involving Human Subjects

A. Research design, anticipated risks and benefits

1. Objectives and rationale

a. Disease to be treated
b. Natural history of disease
c. Alternative treatments

2. Research Methods

a. Structure of genetic material to be inserted
b. Tissue culture and animal studies

3. Clinical and public-health considerations in the treatment of patients

4. Qualifications of investigators, adequacy of laboratory and clinical facilities

B. Selection of subjects

C. Informed consent process

D. The protection of privacy and confidentiality

II. General Social Issues Not Covered by the DHHS Regulations for Research Involving Human Subjects

Example: What effect, if any, is the proposed somatic-cell therapy likely to have on the reproductive cells of treated patients? Please provide laboratory data or bibliographic references that pertain to the answering of this question.

III. Requested documentation

A. Original protocol or grant application

B. Responses to the "Points to Consider"

LeRoy Walters
10/25/84

requirement for use of controls. Drs. Tolin, Arntzen, and Pirone agreed. Dr. Arntzen said a statement concerning use of controls would logically be inserted in item C. Dr. Pirone suggested item C-1 might include a statement to the effect that "data should include information on engineered and control plants." Dr. Scandalios felt the title of Section C should be modified to read:

"Characteristics and Monitoring of Genetically Engineered and Control Plants."

The working group accepted Dr. Scandalios' suggestion.

Dr. Arntzen questioned whether the working group should specifically request that monitoring techniques be described. Dr. Fedoroff felt inclusion of a specific statement was unnecessary; she thought item C-2 was specifically saying "tell us how you monitor." She felt the question of whether the proposed monitoring was adequate should be addressed on a case-by-case basis.

Dr. Scandalios felt the proposed modification and the genetic stability of the inserted DNA should be evaluated. Dr. Tolin said Appendix L-II-C specifies the types of modifications which may be introduced into the test plants under Appendix L. Dr. Lacy felt "changes" could involve deletion as well as insertion of genetic materials. He suggested the term "altered DNA" was more encompassing and should be introduced into item C-2-f. The working group agreed.

Following this discussion the Working Group on Release into Environment agreed the guidance document would read as follows:

"Proposed Guidelines for Submission Under Appendix L.

"Appendix L of the Guidelines specifies conditions under which certain plants may be approved for 'release into the environment' including field tests. Experiments in this category cannot be initiated without submission of relevant information on the proposed experiments to NIH, review by the RAC Plant Working Group, and specific approval by NIH.

"The proposal should include a statement of objectives and a description of materials and methods, including methodology for monitoring the experiments, and expected results. A summary of relevant preliminary results should accompany the proposal. A check list of detailed requirements should include but not be limited to:

"A. Description of Plant Materials.

Give common and scientific names of plants. Identify the specific cultivars or genetic lines to be used. Include information on the relative homogeneity of the plant cultivars or lines and specific genetic markers they are known to possess.

"B. Vectors and Method of Introduction.

"1. Describe the cloned DNA segment and its expression in the new host.

"2. Describe the method(s) by which the proposed DNA vector will be or has been constructed. Diagrams are very helpful and may be necessary for adequate understanding of the construct. Explain the advantages (and disadvantage(s), if appropriate) of your vectors, if other candidate vectors could be considered.

"3. If microorganisms are used to introduce vectors or are vectors themselves, indicate how they compare with wild-type strains. If disabled pathogens are used to transmit the vector, indicate factors that will most likely prevent these microorganisms from regaining or acquiring pathogenic potential. If the vector is likely to survive independently of the desired host(s), refer to this possibility and provide any available data to assess the probability of transfer to other organisms.

"4. If microorganisms are used to introduce vectors, the absence of these microorganisms in the plants to be released in the field should be documented.

"C. Characteristics and Monitoring of Genetically Engineered and Control Plants.

"1. Provide data from greenhouse and/or growth chamber studies to support prospective field studies. Include morphological data for at least two generations of plants if feasible. Supply any molecular or physiological data, especially as applicable to the trait(s) under consideration.

"Specify plant monitoring procedures, frequency, and types of data obtained.

"2. Field plots should meet the criteria specified in Appendix L-II-D:

"Appendix L-II-D. Plants are grown in controlled access fields under specified conditions appropriate for the plant under study and the geographical location. Such conditions should include provisions for using good cultural and pest control practices, for physical isolation from plants of the same species outside of the experimental plot in accordance with pollination characteristics of the species, and for further preventing plants containing recombinant DNA from becoming established in the environment. Review by the IBC should include an appraisal by scientists knowledgeable of the crop, its production practices, and the local geographical conditions. Procedures for assessing alterations in and the spread of organisms containing recombinant DNA must be

developed. The results of the outlined tests must be submitted for review by the IBC. Copies must also be submitted to the Plant Working Group of the RAC.

"Supporting data should include the following:

"a. total area;

"b. geographical location(s): where, how many locations;

"c. plot design: for example, replication, row spacing, nature of border rows;

"d. specify plant monitoring procedures: frequency; types of data to be obtained, including leaf, seed, fruit, or root characteristics; disease and insect population monitoring;

"e. specify techniques for monitoring the vector and/or altered DNA; and

"f. specify access and security measures."

RISK ASSESSMENT WORKSHOP

Dr. McGarrity asked Dr. Tolin for an update on the planned risk assessment workshop. Dr. Tolin said the workshop planned jointly by the NIH and USDA was to review and synthesize available scientific information. She said the NIH-USDA workshop should provide information to RAC in its deliberations and should also benefit RAC working groups such as the Working Group on Release into Environment. Dr. Tolin thought the workshop would focus primarily on plants and associated microorganisms and would most probably be similar in format to the workshop sponsored by the National Institute of Allergy and Infectious Diseases (NIAID) at Pasadena, California.

On April 11-12, 1980, NIAID sponsored in Pasadena, California, A "Workshop on Recombinant DNA Risk Assessment." The workshop was designed to define the scientific issues and assess the potential risks of: (1) possible direct adverse effects of hormone-producing strains of E. coli K-12, and (2) the possible occurrence of autoantibodies or autoreactive cells due to the production of eukarotic polypeptides (including hormones) by E. coli K-12 should such strains for unexpected reasons colonize higher organisms. In order to address these topics, the meeting brought together scientists from the fields of immunology, endocrinology, physiology, microbiology, infectious diseases, and other appropriate disciplines. The information synthesized by the workshop and workshop recommendations to NIAID were used to implement the NIH program to assess the risks of recombinant DNA.

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NEWS FROM CONGRESSMAN ALBERT GORE, JR.

1131 Longworth Office Building Washington, D.C. 20515 Phone: (202) 225-4231

1192

FOR IMMEDIATE RELEASE
October 9, 1984
Contact: Mike Kopp

HOUSE PASSES BILL TO ESTABLISH BIOETHICS COMMISSION

WASHINGTON, D.C. -- The House of Representatives TODAY passed legislation that would establish a Congressional Ethics Advisory Commission to study ethical implications of human genetic engineering and human fetal research.

The legislation, which represents a compromise agreement between legislation sponsored by Congressman Albert Gore, Jr. (D-Tn) and a bill in the Senate, would authorize the Commission to examine a broad range of biomedical issues and report to the Congress and the public.

Gore's legislation initially called for the establishment of a presidential commission to study human genetic engineering. He introduced the legislation on April 27, 1983, following three days of hearings he conducted in late 1982 on the legal, moral and ethical implications of the science.

According to the compromise legislation passed by Congress, the Commission will report on research and developments in genetic engineering and its implications. A seperate Biomedical Ethics Advisory Committee will work with the Commission to help prepare the reports and studies. The Committee's 14 members will be selected from the fields of medicine, behavorial sciences, ethics, theology, law, health adminstration, government and the humanities.

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"Our society is unprepared for the questions that will be forced upon us by human genetic engineering," said Gore. "It is imperative that we monitor more closely these new developments and accelerate the creation of this new body to guide us in making the decisions we will confront."

Ethics Advisory Commission

Conference Agreement:

The conference agreement would change the ethics advisory committee located in the Office of Technology Assessment (OTA) in the Senate bill into an independent Congressional Ethics Advisory Commission patterned after the OTA. The Commission would examine a broad range of biomedical issues and report to the Congress and the public. Two studies are specifically mandated in the legislation: (1) an examination of the nature, advisability, and the biomedical and ethical implications of exercising any waiver of existing Federal protections of human fetuses in research and (2) a study of the ethical implications of developments in genetic engineering for human genetic engineering.

of Diabetes and Digestive and Kidney Diseases

Sec. 11. The Secretary of Health and Human Services shall conduct an administrative review of the disease research programs of the National Institute of Diabetes and Digestive and Kidney Diseases to determine if any of such programs could be more effectively and efficiently managed by other national research institutes. The Secretary shall complete such review within the one-year period beginning on the date of the enactment of this section.

Biomedical Ethics

Sec. 12. Title III (as amended by section 3) is amended by adding at the end the following:

''Part I--Biomedical Ethics

''Sec. 381. (a) There is established in the legislative branch of the Government the Biomedical Ethics Board (hereinafter referred to as the 'Board').

''(b)(1) The Board shall consist of twelve members as follows:

''(A) Six Members of the Senate appointed by the President pro tempore of the Senate, three from the majority party and three from the minority party.

''(B) Six Members of the House of Representatives appointed by the Speaker of the House of Representatives, three from the majority party and three from the minority party.

"(2) The term of office of a member of the Board shall expire when the member leaves the office of Senator or Representative, as the case may be, or upon the expiration of eight years from the date of the member's appointment to the Board, whichever occurs first.

"(3) Vacancies in the membership of the Board shall not affect the power of the remaining members to execute the functions of the Board and shall be filled in the same manner as in the case of the original appointment.

"(4) The Board shall select a chairman and a vice chairman from among its members at the beginning of each Congress. The vice chairman shall act as chairman in the absence of the chairman or in the event of the incapacity of the chairman. The chairmanship and vice chairmanship shall alternate between the Senate and the House of Representatives with each Congress. The chairman during each even-numbered Congress shall be selected by the Members of the House of Representaties on the Board from among their number. The vice chairman during each Congress shall be chosen in the same manner from that House of Congress other than the House of Congress of which the chairman is a Member.

"(5) The Board shall meet once every three months unless such meeting is dispensed with by the chairman, and may meet at any time upon the request of four or more members of the Board or upon the call of the chairman.

``(c)(1) The Board shall study and report to the Congress on a continuing basis on the ethical issues arising from the delivery of health care and biomedical and behavioral research, including the protection of human subjects of such research and developments in genetic engineering (including activities in recombinant DNA technology) which have implications for human genetic engineering.

``(2)(A) Except as provided in subparagraph (B), an annual report shall be transmitted to the Congress identifying the issues which were the subject of the study conducted under paragraph (1) and indentifying areas, programs, and practices of medicine and biomedical and behavioral research which have significant ethical implications and which would be appropriate subjects for study.

``(B) A report on research and developments in genetic engineering (including activities in recombinant DNA technology) which have implications for human genetic engineering shall be transmitted to the Congress not later than eighteen months after the appointment of the committee under subsection (d).

``(d)(1) To conduct the study and make the reports required by subsection (c), the Board shall appoint a Biomedical Ethics Advisory Committee (hereinafter referred to as the `Committee'). The Committee shall consist of fourteen

members as follows:

''(A) Four of the members shall be appointed by the Board from individuals who are distinguished in biomedical or behavioral research.

''(B) Three of the members shall be appointed by the Board from individuals who are distinguished in the practice of medicine or otherwise distinguished in the provision of health care.

''(C) Five of the members shall be appointed by the Board from individuals who are distinguished in one or more of the fields of ethics, theology, law, the natural sciences (other than a biomedical or behavioral science), the social sciences, the humanities, health administration, government, and public affairs.

''(D) Two of the members shall be appointed by the Board from individuals who are representatives of citizens with an interest in biomedical ethics but who posses no specific expertise.

''(2)(A) The Committee, by majority vote, shall elect from its members a chairman and a vice chairman and appoint an executive director who shall serve for such time and under such conditions as the Committee may prescribe. In the absence of the chairman, or in the event of his incapacity, the vice chairman shall act as chairman.

''(B) The term of office of each member of the Committee

shall be four years, except that any such member appointed to fill a vacancy occuring prior to the expiration of the term for which his predecessor was appointed shall be appointed for the remainder of such term. Terms of the members shall be staggered so as to establish a rotating membership.

"(C) The members of the Committee shall receive no pay for their services as members of the Committee, but shall be allowed necessary travel expenses (or, in the alternative, mileage for use of privately owned vehicles and a per diem in lieu of subsistence at not to exceed the rate prescribed in sections 5702 and 5704 of title 5, United States Code) and other necessary expenses incurred by them in the performance of duties vested in the Committee, without regard to the provisions of subchapter 1 of chapter 57 and section 5731 of title 5, United States Code, and regulations promulgated thereunder.

"(D) The executive director of the Committee, with the approval of the Committee, may employ such staff and consultants as necessary to prepare studies and reports for the Committee.

"(3)(A) The Committee may, for the purpose of carrying out its functions, hold such public hearings, sit and act at such times and places, and take such testimony, as the Committee considers appropriate.

"(B) Upon request of the Committee, the head of any

Federal agency is authorized to detail, on a reimbursable basis, any of the personnel of such agency to the Committee to assist the Committee in carrying out its functions.

''(C) The Committee may secure directly from any department or agency of the United States information necessary to enable it to carry out its functions. Upon request of the chairman of the Committee, the head of such department or agency shall furnish such information to the Committee.

''(D) The Committee may accept, use, and dispose of gifts or donations or services or property.

''(E) The Committee may use the United States mails in the same manner and under the same conditions as other departments and agencies of the United States.

''(e) To enable the Board and the Committee to carry out their functions there are authorized to be appropriated $2,000,000 for fiscal year 1985, $2,500,000 for fiscal year 1986, and $3,000,000 for fiscal year 1987.''.

Miscellaneous

Sec. 13. (a) From funds available under section 301 of the Public Health Service Act in fiscal years 1985 and 1986, the Secretary of Health and Human Services, in consultation with the Director of the National Institutes of Health and Commissioner of the Food and Drug Administration, shall make a grant to an academic institution for the establishment and

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

1193

SEP 4 1984

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Honorable Albert Gore, Jr.
Chairman
Subcommittee on Investigations
and Oversight
Committee on Science and Technology
House of Representatives
Washington, D.C. 20515

Dear Mr. Chairman:

This is a follow-up to the Administrator's letter to you of July 23, 1984, concerning a series of specific questions you posed on what EPA plans to do about a proposed field trial of a genetically engineered anti-ice-nucleating microbial pesticide. Your specific questions and our responses are as follows.

(1) Does EPA have jurisdiction under The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) to require that Advanced Genetic Sciences (AGS) obtain an Experimental Use Permit (EUP) for the proposed experiment?

Yes, EPA does have this jurisdiction under FIFRA.

(2) If yes, has EPA (a) evaluated the need for this or any similar experiments, and/or (b) decided that such a permit is or is not required?

EPA scientists are evaluating data on the AGS field experiment proposal that were voluntarily provided to the National Institutes of Health's (NIH) Recombinant-DNA Advisory Committee (RAC). Evaluation of the data made available to EPA has raised a number of questions which may suggest the need for an EUP, but which can only be resolved with additional information on the nature of the genetically engineered organism. In other words, we do not now have sufficient information to determine whether an EUP should be required for the AGS field experiment.

(3) Has AGS or NIH sought out the opinion of EPA as to whether or not an EUP is required, or has EPA informed AGS or NIH of its jurisdiction under FIFRA?

AGS has not sought EPA's position on this issue, and the Agency has not directly informed AGS of its present concerns, although the Agency intends to do so shortly. NIH has requested EPA's comments on various proposals to field test recombinant Pseudomonas syringae. EPA has provided NIH with a summary of its review of the scientific literature and other available information on the proposed experiments.

(4) Does EPA believe that environmental and health questions concerning the safety of the AGS experiment have been sufficiently considered, either by NIH or by EPA, so that the experiment should be permitted to go forward under the appropriate FIFRA and NIH standards?

No, EPA has not concluded that the AGS field experiment should be permitted to go forward. As explained above, the Agency has a number of questions about the proposed experiment, and we need more information than is currently available to answer these questions. With regard to the NIH's own assessment, EPA will carefully consider that assessment in deciding how or whether to regulate pesticides under FIFRA.

(5) How does EPA intend to proceed with respect to the AGS experiment and to any future field scale tests of a pesticide prior to publication of its Federal Register notice?

We have decided to implement the proposal the Administrator discussed in his letter to you last spring to require a several month pre-test notification of EPA for field tests with genetically engineered (and non-indigenous) microbial pesticides. Each notification will include information sufficient to determine whether an EUP, and the data supporting it, should be requested. As I explained in my previous letter, the Agency intends to publish a Federal Register notice which will fully explain our plans for regulating biotechnology under the Toxic Substances Control Act (TSCA) and FIFRA. In light of the current situation with the AGS field experiment, we have decided to publish an additional, earlier Federal Register notice specifically announcing the pre-test notification as an interim procedure, to be followed at least until a more formal approach is established through the later notice. The interim notice will also provide an opportunity for public comment on the issues. This earlier notice, which will appear within the next few weeks, will apply to AGS and any other field experiments with genetically engineered biological pesticides.

With regard to your request for copies of background documents, I enclose the EPA Office of General Counsel's legal opinion on the applicability of FIFRA and TSCA to non-ice-nucleating bacteria, and EPA's August 30, 1984, letter to an attorney for a public interest organization who petitioned the Agency to require an EUP for all intentional releases of genetically engineered biological pesticides.

I hope this information is helpful. If I can be of further service, please let me know.

Sincerely yours,

Marcia Williams

John A. Moore
Assistant Administrator
for Pesticides
and Toxic Substances

Enclosures

U.S. HOUSE OF REPRESENTATIVES

COMMITTEE ON SCIENCE AND TECHNOLOGY

SUITE 2321 RAYBURN HOUSE OFFICE BUILDING
WASHINGTON, D.C. 20515
(202) 225-6371

June 21, 1984

Honorable William D. Ruckelshaus
Administrator
Environmental Protection Agency
401 M Street, SW
Washington, D.C. 20460

Dear Mr. Ruckelshaus:

Thank you for your extensive reply to my letter of March 12 requesting information concerning EPA's plans to regulate biotechnology under FIFRA and TSCA. I recognize that EPA is undertaking a serious effort to sort out the many questions involved in the regulation of biotechnology, and I appreciate the thoughtfulness of your reply.

I am writing at this time in order to better understand EPA's current position on the exercise of its jurisdiction under the Federal Insecticide, Fungicide, and Rodenticide Act as it pertains to the field trials of ice minus bacteria. I am also writing to obtain information abut EPA's intended course of action with respect to the NIH Recombinant DNA Advisory Committee's June 1st recommendation to the NIH Director to approve a field trial of an ice minus bacteria sponsored by Advanced Genetic Sciences (AGS), an industrial concern.

Specifically, I would appreciate answers to the following questions:

1. Does EPA have jurisdiction under FIFRA to require that AGS obtain an experimental use permit (EUP) for the proposed experiment?

2. If yes, has EPA (a) evaluated the need for a permit for this or any similar experiments, and/or (b) decided that such a permit is or is not required?

3. Has AGS or NIH sought out the opinion of EPA as to whether or not an EUP is required, or has EPA informed AGS or NIH of its jurisdiction under FIFRA?

4. Does EPA believe that environmental and health questions concerning the safety of the AGS experiment have been sufficiently considered, either by NIH or by EPA, so that the experiment should be permitted to go forward under the appropriate FIFRA and NIH standards?

5. How does EPA intend to proceed with respect to the AGS experiment and to any future field scale tests of a pesticide prior to publication of its Federal Register notice?

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I would also appreciate receiving copies of EPA documents which bear on EPA's answers to these questions -- for example, any Office of General Counsel memos pertaining to EPA's decision that the ice minus bacteria is or is not a pesticide within the definition of FIFRA; any EPA risk assessment of the AGS's experiment; any EPA decision documents concerning the need for an EUP of the AGS experiment.

I would appreciate a reply to this request on or before July 16. If you have any questions concerning this request, please call Robert B. Nicholas, Chief Counsel/Staff Director of the Subcommittee on Investigations and Oversight. Mr. Nicholas can be reached at 226-3636.

Sincerely,

Albert Gore, Jr.
Chairman
Subcommittee on Investigations
and Oversight

AG/Ntk

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

AUG 30 1984

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Edward Lee Rogers, Esq.
Suite T-200
1718 P Street, NW
Washington, DC 20036

Dear Mr. Rogers:

Your June 15, 1984 petition requested the Agency to require experimental use permits for all recombinant DNA pesticides released into the environment. The Agency is aware of the implications associated with genetic engineering and the potential for problems associated with the release into the environment of novel microbial pesticides.

EPA has regulatory authority over the distribution and use of pesticide products, including microbial pesticides, as specified in the Pesticide Registration Regulations - 40 CFR 162. The Agency has issued a regulation containing data requirements for microbial pesticides (Part 158 - Data Requirements for Registration) and has published guidelines through the National Technical Information Service containing recommended test methods for developing the required data (Subdivision M - Pesticide Assessment Guidelines).

We are also developing procedures and data requirements to address specific issues of health or environmental concern for genetically manipulated microbial pesticides. One issue that has received considerable thought is the need for experimental use permits for performing pesticide evaluations on ten acres of land or less. 40 CFR 172 currently gives the Agency authority to require experimental use permits for certain small scale testing. The Agency under certain circumstances has required an experimental use permit for an experimental program of 10 acres or less.

Until EPA adopts a more formal approach to these substances, notification will be required as an interim procedure for small scale field studies conducted with novel microbial pesticides. Based on the information contained in the notificiation, the Agency will determine whether an EUP is required. In the process of determining the need for an EUP, the Agency may solicit the advice of expert individuals or committees. Such expert advice may be solicited both on general issues related to review procedures and on specific pesticide uses.

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EPA is a non-voting member of the National Institutes of Health (NIH) Committee which deals with recombinant DNA issues. As such, its representative has been involved with the committee and its extensive deliberation concerning several Psuedomomas syringae experiments. I view these important activities as initiatives between NIH and those submitting the experimental protocol; it does not supplant the need to notify the Office of Pesticide Programs. It is clear that the Agency would carefully study the opinions of the NIH Committee in formulating its response under the statutory requirements of the Federal Insecticide, Fungicide and Rodenticide Act.

In response to your specific concern about a disease resistant plant generated through recombinant DNA techniques, it does not appear that this product falls under the purview of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA). Higher plants, regardless of how produced, would not come within the scope of FIFRA, unless they were considered to be pesticides. EPA has not in the past considered any of the many disease resistant plants in commerce to be pesticides. Therefore, it is unlikely that the experimental use provisions of 40 CFR §172 are applicable in this case.

Your concerns expressed in the petition are similar to many of those already under consideration within the Agency. Be assured that the information that you have supplied and the points you have raised will be carefully considered. Thank you for your interest and concern.

Sincerely yours,

John A. Moore
Assistant Administrator
for Pesticides
and Toxic Substances

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BERKELEY, CALIFORNIA 94720

1194

October 17, 1984

Dr. William J. Gartland
Executive Secretary, RAC
National Institute of Allergy
and Infectious Diseases
National Institutes of Health
Bethesda, MD 20205

Dear Dr. Gartland:

Mr. Rifkin's proposed amendment would put an end to the molecular study of the nature of the genetic barriers between mammalian species.

Much remains to be learned about those barriers (Ferris *et al.*, 1983a). Their study will give us a deeper understanding of the nature of species and the process of evolution. In particular, interspecific transfer of genes will allow testing of ideas about the nature of species differences and the forces that mold the gene pools of species.

Evolution is a process that affects all species. What controls its rate (which is very high in many mammals) and direction is only now beginning to be understood as the result of molecular genetic studies. NIH and NSF have an obligation to society to foster research into the nature of this fundamental biological process.

Yours sincerely,

Allan C. Wilson
Professor of Biochemistry

ACW/k
Encl. Ferris *et al.*, 1983a
cc: Dr. Ruth L. Kirschstein

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Genetics

Flow of mitochondrial DNA across a species boundary

(European mouse populations/restriction enzymes/cleavage maps/protein electrophoresis/hybrid zone)

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Communicated by Ernst Mayr, December 21, 1982

ABSTRACT **Restriction analysis shows that wild Scandinavian mice belonging to the species *Mus musculus* contain the mitochondrial DNA of a neighboring species, *M. domesticus*. This demonstration results from comparisons of Scandinavian mice with authentic *M. domesticus* and *M. musculus* from other parts of Europe. Electrophoretic and immunological analysis of eight diagnostic proteins confirms that mice from north of the hybrid zone in Denmark are *M. musculus* in regard to their nuclear genes. In contrast, the mice tested from this region and a nearby part of Sweden have exclusively *M. domesticus* types of mitochondrial DNA. Phylogenetic analysis of the restriction maps suggests that the mitochondrial DNAs found in Scandinavian *M. musculus* could stem from a single *M. domesticus* female.**

The growing use of mtDNA as a tool for genetic research on animal populations (1, 2) makes it important to compare the ability of nuclear and mitochondrial genomes to move between populations. [mtDNA differs conspicuously from nuclear DNA not only by being outside the nucleus but also by existing in thousands of copies per cell, being inherited maternally, and evolving quickly (3, 4).] Such a comparison can be made by examining the distribution of genes across a hybrid zone—i.e., a geographic zone where two species meet and interbreed but where there is limited flow of nuclear genes (5).

Of all the hybrid zones examined by both organismal and molecular biologists, that between two species of mice in Denmark is the best known (6–8). The comprehensive study by Hunt and Selander (7) of proteins encoded by the nuclei of 2,696 mice caught at 44 Danish localities delineated the hybrid zone as regards nuclear genes. In addition, the protein evidence agrees with anatomical evidence as to the geographic location of this hybrid zone (6–8).

Further protein work has shown how these Danish mice are related to other commensal mice (9, 10). Commensal mice are those species that live in close association with buildings used by humans. They contrast with aboriginal mice (in Europe: *Mus spretus*, *M. hortulanus*, and *M. abbotti*), which live predominantly independent of human dwellings and, in nature, do not interbreed with commensal mice (10–12). According to a phylogenetic analysis of the protein data, there are two commensal mouse species in Europe. One, known as *M. domesticus*, lives in southern Denmark, in most of the rest of western Europe, and around the Mediterranean Sea (11, 12) (see Fig. 1). The second, *M. musculus*, lives in northern Denmark, the rest of Scandinavia, and eastern Europe (11, 12). The hybrid zone defined by Ursin (6) and Selander and co-workers (7, 8) is the meeting place of *M. domesticus* and *M. musculus* in Denmark (see Fig. 1). These two types of mice are sometimes considered as semispecies. Our decision to refer to them as separate species is based not only on extensive morphological and biochemical evidence (10–12) but also on the observation that there is a high incidence of sterility in the male offspring of crosses between *M. musculus* females and males from laboratory strains of *M. domesticus* (13).

Mice are also appropriate for comparing mitochondrial and nuclear gene flow because much is already known about their mtDNA. Bibb *et al.* (14) worked out the complete nucleotide sequence for mtDNA from a common laboratory strain of *M. domesticus*, and genetic variation in the mtDNA of mice from various localities in Europe, North Africa, and the Near East has been surveyed (1, 15, 16).

This paper reports the use of restriction enzymes to compare mtDNA from mice collected in the vicinity of the Danish hybrid zone with mtDNA from authentic *M. domesticus* and *musculus* populations collected elsewhere. We also made a parallel study of proteins encoded by the nuclei of these mice. The results of the two studies contrast sharply.

MATERIALS AND METHODS

Mice. Most of the mice examined were trapped in the wild or were descendants of wild individuals caught within the last 10 years at 13 localities, 11 of which are shown on the map (Fig. 1). An inbred strain of *M. domesticus* (DBA/2, from National Institutes of Health) was included for reference.

mtDNA Comparisons. mtDNA was purified to homogeneity from single animals and then digested with three restriction enzymes (*Xba* I, *Mbo* I, and *Hin*fI from New England BioLabs); fragments were labeled at the ends with ^{32}P, separated electrophoretically in 1.2% agarose or 3.5% polyacrylamide gels, and detected with x-ray film (1). The sizes of the fragments were estimated by comparison with the known sizes of the fragments of old inbred mtDNA, whose complete base sequence is established (14). By considering these fragment sizes in relation to those predicted by the known sequence, we constructed cleavage maps for about 70 cleavage sites in each of the *M. domesticus*-like mtDNAs and about 40 cleavage sites in each of the *M. musculus* mtDNAs.

To estimate the percentage divergence between base sequences of pairs of mtDNAs, we used two approaches. The first, based on map comparisons, uses equation 16 of Nei and Li (17), which assumes that there is heterogeneity among cleavage sites with respect to the probability of base substitution. This assumption has been validated by recent sequence studies (18). The second approach, based on the fraction of shared fragments, uses equation 20 of Nei and Li (17), which assumes homogeneity among cleavage sites with respect to the probability

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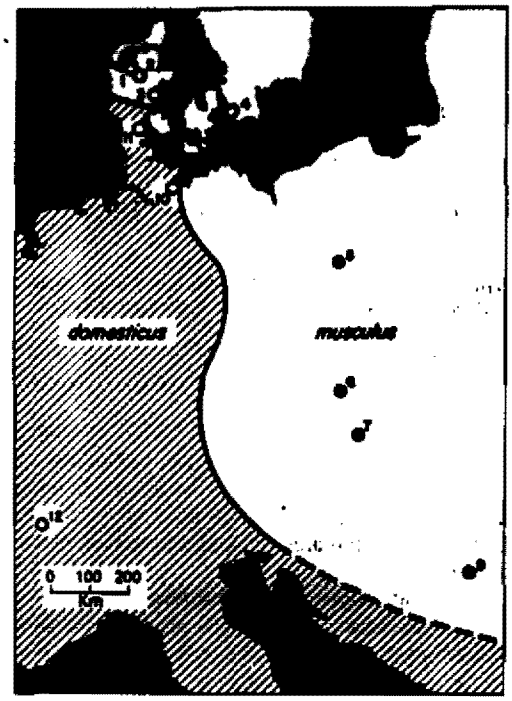

FIG. 1. Map of a part of Europe showing the distribution of the two commensal species of house mice, *M. domesticus* and *M. musculus*, and their mtDNAs. The two species meet and hybridize in a narrow zone, indicated by the thick line, extending from Denmark through Central Europe to the Black Sea (7, 9). The numbers refer to localities where mice were collected for this study. On the *M. musculus* side of the hybrid zone are Skive (*1*), Viborg (*2*), and Hov (*3*), northern Denmark; Malmö (*4*), Sweden; Turow (*5*), Poland; Brno (*6*) and Bratislava (*7*), Czechoslovakia; Halbturn (*8*), Austria (not shown because these mice were analyzed for proteins encoded by the nucleus but not for mtDNA); and Belgrade (*9*), Yugoslavia. On the *M. domesticus* side of the hybrid zone are Lübeck (*10*), Federal Republic of Germany; Haderslev (*11*), southern Denmark; Nyon (*12*), Switzerland; and Giza (*13*), Egypt (not shown). The empty and solid circles mark sites of occurrence of *M. domesticus*-like and *musculus* mtDNA, respectively.

of base substitution and takes no account of back mutations. Because both approaches ignore the fact that transitions occur more often than transversions (18), they can underestimate the extent of point mutational divergence. However, the degree of underestimation is slight for sequences that differ by <5%. For closely related mtDNAs, sequence determination and restriction analysis generally produce very similar estimates of sequence divergence, provided that at least 40 restriction sites are examined per mtDNA (18).

Protein Comparisons. From an electrophoretic study of 56 protein-encoding loci in mouse populations (10), we selected seven loci for their power to discriminate between the *M. domesticus* and *musculus* species. The preparation of tissue extracts and the electrophoretic methods of separating and detecting enzymes were described by Sage (19). Genetic variants of immunoglobulins were surveyed by testing mouse sera in solid-phase radioimmunoassays for reactivity with 18 monoclonal antibodies, which were directed against products of three immunoglobulin loci (*Igh-1*, *Igh-3*, and *Igh-4*) (20). *Igh-3* was chosen for its superior ability to discriminate between *M. domesticus* and *musculus*.

RESULTS

mtDNA Comparisons. Table 1 lists the fragment sizes (in base pairs) observed electrophoretically after digesting mtDNA from 36 mice with three restriction enzymes. Twenty-three

Table 1. Sizes of fragments produced by digestion of mouse mtDNA with three restriction enzymes

M. domesticus-like					*M. musculus*			*M. spretus*
	A	B			C	D		E
	7576	7576			5066	9066		9361
	5066	5066			3994	3994		5066
	1923	2378			3241	3582		934*
	934	934			1254	1254		
	455	341			934	934		
	341				669	669		
					455	455		
					341*	341		
A	D	F	I	K	L	M	N	P
2009	2009	2009	2009	2009	2009	2009	2009	1400
1608	1819	1724	1608	1608	1608	1608	1608	1310
1372	1344	1372	1564	1564	1530	1530	1372	1200
1344	885	936	1344	1344	1372	1452	1350	1020
845	845	845	845	845	1080	1080	1080	1000
772	772	772	772	772	845	845	845	655
705	705	705	705	705	772	772	772	635
598	598	598	598	598	705	705	683	630
581	581	581	581	581	598	598	598	620
533	533	533	529	529	533	533	581	610
529	529	529	488	488	520	520	533	598
488	488	488	468	468	488	488	488	591
468	487	468	461	461	478	478	478	529
461	468	461	444	444	468	468	468	478
439	461	439	439	369	450	450	450	468
369	439	408	369	343	369	369	369	461
343	369	369	343	320	297	327	297	435
340	343	343	320	301	269	297*	269	410
301	340	340	301	297	259	269	259	389
297	301	301	297	279	255	259	255	337
259	297	297	259	259	222	255	222	335
222	259	259	222	222	211	211	211	295
211	222	222	213	213	147	147	192	255
192	192	192	211	211	120	120	147	219
155	155	155	155	160	112	112	120	214
147	147	147	147	155	105	95	112	192
120	120	120	120	147	95	88	105	182
105	105	105	105	120	88	67	95	147
104	104	104	95	105	80	63	88	145
95	95	95*	88	95	67	55	67	112
88	88	88	67	88	63	34†	63	104
67	67	67	63	67	55†	31†	55†	88
63	63	63†	34†	63	34†		34†	85
34	34†	34†	31†	34†	31†		31†	67
31	31†	31†		31†				63
								34†
								31†
A	E	I	L	O	P	Q	R	S
1993	1993	1734	1993	1734	2248	2248	2248	1993
1734	1734	1631	1734	1631	1993	1653	1993	1140
1329	1026	1329	1459	1459	1370	1370	1370	1026
1026	946	1326	1329	1329	1026	1026	1026	980
946	920	1026	1242	1026	880	880	950	935
920	879	946	1030	946	855	650	855	920
879	713	920	946	879	638	638	638	905
638	638	638	879	638	539	539	539	765
539	539	539	732	533	505	505	505	732
533	533	533	638	497	493	493	493	638
497	497	497	485	489	489	489	489	630
489	489	489	480	485	485	485	485	575
485	485	485	447	480	480	480	480	533
480	480	455	417	447	450	450	450	485
447	447	417	405	417	447	447	447	463
417	417†	405	399	399	383	383	383	460
399	416†	399	368	368	368	368	368	447
368	405	368	367	367	360	360	360	417
367	399	367	318	362	355	355	355	383
318	368	362	212	318	318	340	318	368
263	367	318	195	263	243	318	243	333
243	318	243	144	243	216	243	216	225
216	243	216	67†	216	212	216	212	216
212	216	212	9†	212	203	212	203	212
195	212	195		195	190	205	190	190
144	200	144		144	98	203	98	180
94	195	67†		94	90	190	90	95
67	144	25†		67	73	185	73	9†
48	67	9†		48	70	90	67	
9†	9†			9†	67	73	52	
					52	70	9†	
					9†	67		
						52		
						9†		

Sizes of fragments produced by *Xba* I (*Top*), *Mbo* I (*Middle*), and *Hin*fI (*Bottom*) are shown in base pairs.

*Two fragments of this size are predicted from the band intensity and comparison with the nucleotide sequence of old inbred mtDNA (14).

†Fragments too small to be observed routinely with the present method (or fragments of nearly identical size that give overlapping bands) but predicted from the cleavage maps (Fig. 3).

Table 2. Quantitative comparison of fragment patterns for mouse mtDNA

Population	No. of mice	Fragment patterns	Difference matrix: Scandinavian 1	2	3	4	*M. musculus* 5	6	7	9	*M. domesticus* 10	11	12	13	14
Scandinavian															
Skive (1)	1	BIL	—	0	3	3	67	68	71	68	6	28	40	32	28
Viborg (2)*	1	BIL	0	—	3	3	67	68	71	68	6	28	40	32	28
Hov (3)	22	AIL	0.2	0.2	—	0	66	67	70	67	3	25	37	29	25
Malmö (4)	1	AIL	0.2	0.2	0	—	66	67	70	67	3	25	37	29	25
M. musculus															
Poland (5)	1	DNP	5.7	5.7	5.5	5.5	—	11	16	15	67	60	67	63	56
Czechoslovakia (6)	1	CLP	5.7	5.7	5.6	5.6	0.6	—	11	12	68	64	70	66	60
Czechoslovakia (7)	1	DLQ	6.0	6.0	5.9	5.9	1.0	0.6	—	17	71	65	71	69	63
Yugoslavia (9)	2	DMR	6.0	6.0	5.9	5.9	0.9	0.7	1.1	—	68	66	72	66	62
M. domesticus															
W. Germany (10)	1	AKL	0.3	0.3	0.2	0.2	5.6	5.7	6.0	5.9	—	28	40	32	28
S. Denmark (11)	1	AAO	1.9	1.9	1.7	1.7	4.5	4.9	4.9	5.3	2.0	—	20	20	6
Switzerland (12)	1	AFI	3.0	3.0	2.8	2.8	5.3	5.7	5.7	6.1	3.0	1.8	—	22	20
Egypt (13)	1	ADE	2.3	2.3	2.1	2.1	4.8	5.0	5.4	5.3	2.3	1.8	1.5	—	14
Inbred (14)	1	AAA	1.9	1.9	1.7	1.7	4.1	4.4	4.7	4.8	2.0	0.4	1.3	0.9	—

The mouse mtDNAs examined come from populations 1–13 (Fig. 1) and the inbred mouse (14). The single letters identify, from left to right, the fragment patterns listed in Table 1 for the enzymes *Xba* I, *Mbo* I, and *HinfI*. The upper right half of the matrix gives the number of fragment differences. Estimates of the percentage difference in nucleotide sequence shown in the lower left half were made with equation 20 of Nei and Li (17). Similar values were obtained by comparing the mtDNA maps with equation 16 of Nei and Li (17).
*The patterns reported earlier (1) for Viborg mtDNA were in error.

fragment patterns were observed, each being designated by a capital letter. In each case, the summed sizes of the fragments produced by a given enzyme equals about 16.3 kilobases, which corresponds to one mitochondrial genome (14). The total number of fragments observed in the three digests, and hence the average number of restriction sites examined, is ≈70 for a typical mtDNA.

Table 2 gives the correspondence between mice and fragment patterns; there are 11 types of mtDNA in the commensal mice examined. The upper right part of Table 2 shows the number of fragments that were different for each pair of mtDNAs. The five types of mtDNA from authentic *M. domesticus* mice differed from each other by the presence or absence of 6–40 fragments. [This extent of variation among *M. domesticus* mice is representative of the results obtained from a study of a much larger sample ($N > 100$). Some of the results of this larger study appear in ref. 1; all will be reported in a comprehensive paper on the genealogical relationships among wild and laboratory strains of *M. domesticus*.] Likewise, the authentic *M. musculus* mtDNAs differed by 11–17 fragments from one another. In contrast, there are 56–72 fragment differences between the mtDNAs of authentic *M. domesticus* and *musculus*.

mtDNAs from Scandinavian localities on the *musculus* side of the hybrid zone are extremely similar to one another. Only two types, differing from each other by three fragments, were

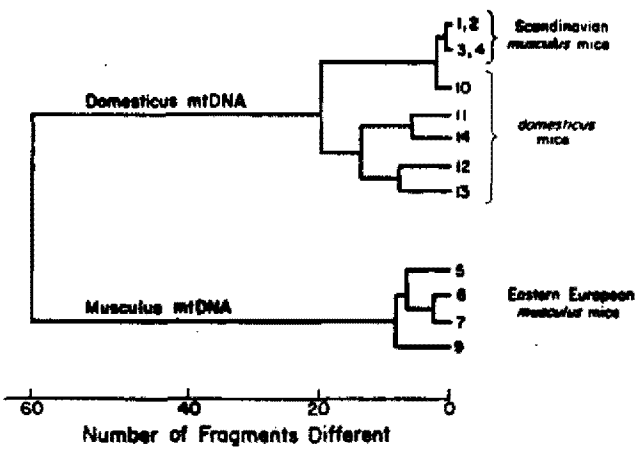

FIG. 2. Tree showing the close genealogical relationship of mtDNA from Danish mice to mtDNA from authentic *M. domesticus*. The tree was built with the parsimony method (21), by considering the fragment sizes in Table 1 as characters. This tree-building method, it should be emphasized, does not assume that the rate of mtDNA evolution is constant. To obtain a root for the tree, we used the mtDNA of *M. spretus*. The most parsimonious tree (shown here) requires 115 changes in character state. By contrast, an alternative tree which derives the Scandinavian mtDNAs from the *M. musculus* mtDNA lineage requires 27 more changes.

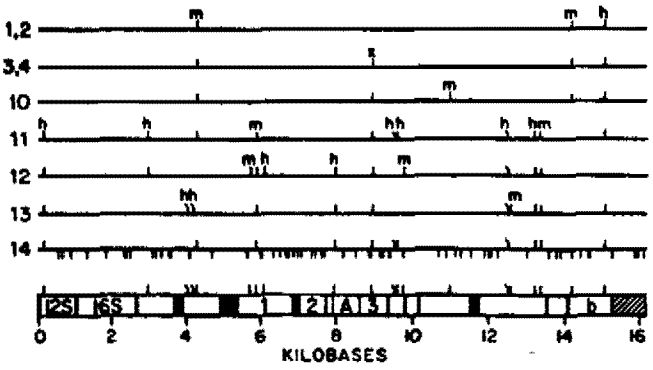

FIG. 3. Genetic maps for variable and constant cleavage sites in *M. domesticus* mtDNAs. The sites were mapped by the method of Cann *et al.* (2) and with reference to the published sequence for a laboratory mouse (14). The numbers 1–13 on the left indicate localities at which the mice were collected (see Fig. 1). Map 14 is for the laboratory mouse (patterns A in Table 1), and it shows below the line the 60 cleavage sites conserved in all the *M. domesticus*-like mtDNAs examined. The marks above each horizontal line indicate variable sites: *m*, *Mbo* I; *h*, *HinfI*; *x*, *Xba* I. The maps are oriented with the origin of replication at 0. The bar shows the locations of the mitochondrial genes of known function: black areas indicate tRNA genes or spacers; 1, 2, and 3 are cytochrome oxidase genes; A is the ATPase gene; and b is the cytochrome *b* gene. The marks on the top of the bar show the 20 variable cleavage sites at which the seven maps differ.

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found among the 25 mice examined (Table 2). Moreover, they differ only slightly from an authentic *M. domesticus* type of mtDNA (from locality 10). More recent results show that one of the Scandinavian mtDNA types (from localities 3 and 4) occurs also in a *M. domesticus* mouse from Cittaducale in central Italy. For these reasons, we consider the known Scandinavian types of mtDNA to belong in the *domesticus* category.

Tree analysis confirms the idea of a genealogical relationship between the mtDNAs of all Scandinavian mice tested and those of authentic *M. domesticus*. Fig. 2 shows the most probable order of branching of the lineages leading from a common ancestor to the 11 types of mtDNA. Alternative trees that ally the mtDNAs of northern Scandinavian mice (from localities 1–4) with authentic *M. musculus* mtDNAs require at least 27 more fragment changes than does the tree shown. The mtDNA tree indicates that the two northern Scandinavian lineages are highly related to each other and to the *M. domesticus* lineage from locality 10 and implies that the two northern Scandinavian types of mtDNA could be each other's closest relatives.

Cleavage maps were constructed for the *M. domesticus*-like mtDNAs (Fig. 3) by relating the fragment patterns to the known sequence of the old inbred type of mouse mtDNA (14). All of the differences in fragment patterns could be accounted for by base substitutions at a total of 20 cleavage sites, with no evidence for any large deletions or additions of DNA (i.e., >20 base pairs). The 20 variable sites are scattered widely in the genome, as has been observed in comparisons of mtDNAs from other closely related mammals (2). We also located numerous cleavage sites in *M. musculus* mtDNAs, obtaining complete maps for *Xba* I and partial maps for *Mbo* I and *Hin*fI, which establish that *M. musculus* mtDNAs have about the same overall length (16.3 ± 0.1 kilobases) as *M. domesticus* mtDNA. Therefore, the mtDNA differences within and between the two species likely arose by the usual process of point mutational divergence.

The lower left part of Table 2 gives estimates of the percentage divergence in nucleotide sequence among all these mitochondrial genomes. Besides emphasizing the *domesticus*-like character of the Scandinavian mtDNAs, these estimates draw attention to the large sequence divergence between authentic *M. musculus* and *domesticus* mtDNAs, ~5%. This value of 5% agrees with our expectation, which is based on the degree of nuclear DNA difference between the *domesticus* and *musculus* species and on the assumption that mtDNA consistently evolves faster than nuclear DNA. A comparison of humans and chimpanzees has shown that in them, as in other primates, mtDNA evolves 5 to 10 times faster than does nuclear DNA (18). The genetic distance between *M. domesticus* and *musculus* proteins (encoded by nuclear DNA) is about half as big as that between humans and chimpanzees (7, 10, 22). Likewise, the extent of mtDNA divergence for these two mouse species is about half of that between humans and chimpanzees (18). It follows that, for mice, mtDNA divergence has probably been 5 to 10 times faster than nuclear DNA divergence.

Protein Comparisons. The results of our protein comparisons contrast sharply with the mtDNA findings. For several populations of mice, we examined the allele frequencies for eight protein-encoding loci which can easily distinguish between *M. domesticus* and *musculus*. In confirmation and extension of previous studies (7, 10), we found that at every one of these loci, the Scandinavian mice (from localities 1–3) resemble *M. musculus* more closely than *M. domesticus* (Table 3). Tree analysis also emphasizes the close relationship of the proteins of northern Scandinavian mice to those of authentic *M. musculus* (Fig. 4). Furthermore, each of the 14 mice sampled at localities 1–3 appears to be fully *M. musculus* as regards alleles at the eight

Table 3. Genetic variation at eight protein loci in mice

Protein-encoding locus	Allele	Allele frequency, % Danish 1–3	*M. musculus* 6–9	*M. domesticus* 12–14
Adh	1	7	5	100
	2	89	95	0
	3	4	0	0
Est-1	1	100	100	4
	2,3	0	0	96
Est-2	1	7	5	100
	2	4	90	0
	3	89	5	0
Est-D	1	4	25	82
	2	0	0	18
	3	96	75	0
Idh-s	1	100	100	22
	2	0	0	78
*Igh-3**	16	29	25	100
	23,24	71	75	0
Mpi	1	100	100	0
	2	0	0	100
Pnp	1,2	0	0	100
	3,4	86	0	0
	5	11	65	0
	6	3	0	0
	7	0	35	0

The Danish mice were from three localities (1–3) on the northern side of the hybrid zone; the other mice were from localities (6–14) far from the boundary between *M. domesticus* and *musculus* (see Fig. 1), or from the inbred strain DBA/2 (1). The proteins examined (and the loci that encode them) were alcohol dehydrogenase (*Adh*), esterase 1, 2, and D (*Est*-1, -2, and -D), isocitrate dehydrogenase (*Idh-s*), immunoglobulin 3 (*Igh-3*), mannose phosphate isomerase (*Mpi*), and purine nucleotide phosphorylase (*Pnp*). A preliminary analysis of the locus encoding esterase-1 shows the *M. domesticus* from localities 10 and 11 to have allele *2*, which predominates in other *M. domesticus*, and the *M. musculus* from locality 4 to have allele *1*, as in other *M. musculus*. Sample sizes for the 10 tabulated populations are 1, 1, 12, 1, 1, 1, 7, 9, 15, and 1.

* For immunoglobulin, phenotypic rather than allelic frequencies are reported. Sample sizes for the tabulated populations are 1, 1, 12, 4, 1, 0, 3, 1, 8, and 1 (population 8 was not examined).

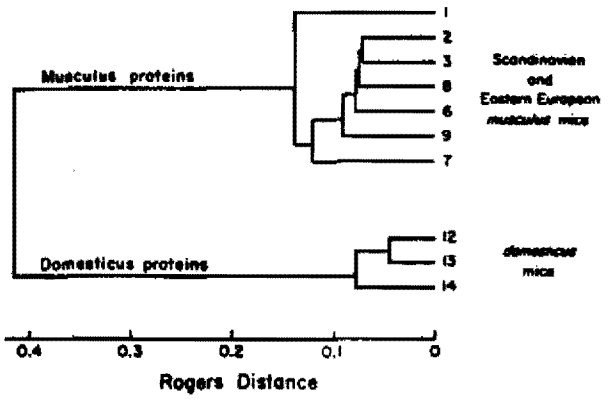

FIG. 4. Tree showing the close relationship of protein loci from Danish mice to those of authentic *M. musculus*. The tree was built by the distance Wagner method (23) from a matrix of Rogers distances (24) based on allele frequencies examined in 10 populations for seven of the eight diagnostic proteins (Table 3); because the immunoglobulin results are phenotypic frequencies, they were omitted. The length of this tree is 1.536. An alternative tree having the topology shown in Fig. 2 (and lacking sample 8) is of length 1.733 and, therefore, is less parsimonious.

diagnostic loci. The results support the conclusion that at none of the diagnostic loci has there been extensive introgression of *M. domesticus* nuclear genes into the *M. musculus* populations sampled in northern Denmark. We recognize that our present sample sizes are too small to allow detection of a low level of nuclear gene flow across the hybrid zone.

DISCUSSION

The ability of mtDNA from one species to invade another species and displace the resident mtDNA is not without precedent. A laboratory strain of mice, KL/oci, which belongs to the species *M. molossinus* with regard to its nuclear genes, has lost *M. molossinus* mtDNA and gained the old inbred type of mtDNA from *M. domesticus* during the past 15 years (1). The present study shows that interspecific transfer of mtDNA can take place in the wild as well. Yonekawa *et al.* (16) independently discovered that mtDNA from northern Danish mice is more related to that of *M. domesticus* than to that of eastern European *M. musculus*, but they did not point out the significance of this finding.

If the flow of organelle DNA between populations that exchange scarcely any nuclear DNA turns out to be common, it will have consequences for the definition of biological species. Traditionally, the biological species is defined as a group of individuals whose common gene pool is protected against the inflow of alien genes (25). While in no way suggesting that this biological species concept will have to be abandoned, we do foresee the possible need for defining species in terms of their nuclear genes.

Our limited survey has revealed only two closely related types of *M. domesticus* mtDNA in the *M. musculus* mice of Scandinavia. These two types could be the result of one colonization event, involving a single *M. domesticus* individual that entered *M. musculus* territory long enough ago to allow two of the descendant lineages to have diverged slightly in nucleotide sequence. A fuller survey will reveal how far *M. domesticus* mtDNA extends into *M. musculus* territory and whether, indeed, we are dealing with a single colonization event. It also should be possible to estimate from the magnitude of the nucleotide sequence diversity when the colonization event or events occurred. Assuming a divergence rate of 2–4% per 1×10^6 years for mtDNA (18), we already can estimate from the restriction data that the *M. domesticus* types of mtDNA in *M. musculus* territory had a common ancestor within the past 100,000 years, a time which is far more recent than that estimated for the divergence of *M. domesticus* and *musculus* mtDNAs (i.e., at least 1×10^6 years). Nucleotide sequence data will permit more accurate estimates of these times.

Experiments aimed at identifying the factors responsible for the replacement of *M. musculus* mtDNA by *M. domesticus* mtDNA in the Scandinavian mice should look for a possible selective or replicative advantage of *M. domesticus* mtDNA, as well as at the reproductive behavior and success of the two species of mice when they come into contact.

We thank L. A. Herzenberg for monoclonal antibodies and facilities; A. Gropp, H. Hoogstraal, W. Z. Lidicker, and I. Savić for providing mice; and R. L. Cann, F. H. C. Crick, K. Fischer Lindahl, D. M. Green, U. Gyllensten, W. Z. Lidicker, E. Mayr, J. L. Patton, E. M. Prager, R. K. Selander, M. Slatkin, M. Stoneking, and T. Uzzell for discussions. This work, a preliminary account of which appeared last year (26), was supported by grants from the National Science Foundation and the National Institutes of Health.

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3601 4th Street
Lubbock, TX 79430
October 23, 1984

Director
Office of Recombinant DNA Activities
Building 31, Room 3B10
National Institutes of Health
Bethesda, Maryland 20205

Re: Jeremy Rifkin Amendments Proposed to NIH Guidelines for Research Involving Recombinant DNA Molecules

To Whom It May Concern,

We, the undersigned, are faculty members of the Texas Tech University Health Sciences Center acting as individuals and are scientists who conduct research in the biomedical sciences sponsored by a variety of granting agencies including the National Institutes of Health. We would like to express to you as strongly as possible our concern that the above two amendments (published as part of the Federal Register, pg. 37016) sponsored by Jeremy Rifkin of the Foundation of Ecomonic Trends do not become part of the NIH Guidelines for Research Involving Recombinant DNA Molecules.

The Guidelines, as they are now written, more than adequately govern this aspect of work with recombinant DNA molecules. If these amendments were to become part of the NIH Guidelines, they would place impossible restrictions upon this type of research. Consequently, work directed at understanding the mechanisms which control normal and abnormal gene expression would be severely limited. For example, molecular genetic studies on the basic research in cancer, cell growth, cell differentiation and development would be limited to those approaches which we now have available, and so new ideas would be inhibited. The newer approaches, which the two amendments would ban, offer insights into fundamental questions of biology and the biomedical sciences that cannot be approached through other methods currently in use. Ultimately, the benefit to medicine and the potential to alleviate human suffering through research using recombinant DNA in this manner will far outweigh the emotional concerns raised by this well-intentioned watch dog group.

Sincerely yours,

UNIVERSITY of PENNSYLVANIA

DEPARTMENT OF HUMAN GENETICS

ROY D. SCHMICKEL, M.D.
Chairman
215-898-3582

The School of Medicine/G3
37th and Hamilton Walk
Philadelphia, PA 19104

October 2, 1984

Dr. William Gartland
Executive Secretary, RAC
National Institute of Allergy
and Infectious Diseases
National Institutes of Health
Bethesda, MD 20205

Dear Dr. Gartland:

I am writing in response to the request from Dr. Jeremy Rifkin to place an amendment to the NIH guidelines for Recombinant DNA Experimentation.

I am concerned that any regulation which would proscribe the study of particular forms of gene expression would greatly limit our ability to design experiments necessary for health research. The ability to transfer genes from one organism to another has been the basis of some of the most dramatic advances in science. Somatic cell hybrids are used routinely to increase our knowledge of the human genetic map. To date, the the somatic cell hybrids are also one of the most efficient ways to isolate particular chromosomes or parts of chromosomes. By such means in somatic cells, the actions of genes can be observed at the cellular level. The transfer of genes to germ cells permits the observation of genes at the organismal and embryological level. This research promises to help us to solve the diseases and misfortunes of hormonal imbalance and birth defects.

The use of interspecies constructs has proven to be extremely useful and permits a careful analysis of small differences between species. The work by Ralph Brinster here at the University of Pennsylvania has been extraordinary in its productivity and represents one of the most fruitful avenues of investigation of hormone action. Only when a gene is injected into germ cells can the effect of the gene be seen in an entire organism, and only when a human gene has been injected into another mammal can we ethically study the embryological action of a human gene. When we consider the enormous number of diseases that are caused by hormonal deficiencies or abnormalities, it is imperative that we continue this type of study of hormonal genes. It is not difficult to look ahead slightly to see the enormous impact that such experiments will have in helping us understand ways to prevent developmental birth defects.

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It is difficult to appreciate Dr. Rifkin's concern for interspecies genetic experiments. Undoubtedly viruses have been transferring genes between mammalian species for millions of years. An amendment to an NIH guideline cannot serve to protect the "integrity of every mammalian species". There is no evidence that nature has established impenetrable species borders and there is direct evidence of the transfer of genetic information between species. The literature on the action of retroviruses stands as testimony to the free and constant transfer of genetic information between species. It is presumptuous for Mr. Rifkin to speak for nature and the "telos" of species. Certainly there are ethical systems which support the expansion of knowledge, the dissolution of ignorance, and the prevention of "natural" tragedies. "Integrity" does not necessarily apply to legislative efforts to freeze a changing universe.

All of humanity can benefit from the knowledge of gene expression and gene control. This is the first time that man has a reasonable hope to attack the evils of developmental defects which cause severe mental retardation and incapacitating physical deformities. It is my hope that the NIH Recombinant DNA Advisory Committee will not accept such presumptuous amendments as that of Jeremy Rifkin, which would hamper the progress of careful and thoughtful research.

Sincerely yours,

Roy Schmickel

Roy D. Schmickel, M.D.

RDS:lc

202

University of Illinois
at Urbana-Champaign

College of Veterinary Medicine
2001 South Lincoln Avenue
Urbana
Illinois 61801

Department of Veterinary Pathobiology
217 333-2449

October 10, 1984

Director
Office of Recombinant DNA Activities
Bldg. 31, Rm. 3B10
National Institutes of Health
Bethesda, MD 20205

Dear Sir/Madame:

I wish to raise the strongest possible objections to the proposals submitted by Mr. Jeremy Rifkin as announced in the Federal Register (49:84:37016-37017). The proposals from Mr. Rifkin are scientifically, morally and ethically flawed. They will serve no useful purpose for the general public. Mr. Rifkin is unaware or chooses to ignore the fact that there is significant evidence that spontaneous gene transfer among mammals occurs.

Sincerely,

John A. Shadduck, DVM, PhD
Professor and Head

JAS:tls

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THE JOHNS HOPKINS UNIVERSITY
SCHOOL OF MEDICINE
and
THE JOHNS HOPKINS HOSPITAL

DEPARTMENT OF PEDIATRICS
JOHN W. LITTLEFIELD, M.D.
Chairman and Pediatrician-in-Chief

Mailing Address:
The Children's Medical & Surgical Center
THE JOHNS HOPKINS HOSPITAL
Baltimore, Md. 21205
Tel: (301) 955-5976

October 4, 1984

William J. Gartland, M.D.
Executive Secretary, RAC
National Institute of Allergy
and Infectious Diseases
National Institutes of Health
Bethesda, MD 20205

Dear Bill:

From several directions I have heard of Mr. Jeremy Rifkin's letter of August 21, 1984 suggesting a prohibition on the transfer of genes between any mammalian species and the germ line of another. I am writing in order to be included in the opposition to such a prohibition. It is unreasonable in my opinion to object to introducing human genes into the eggs of mice or other non-human mammals. Such work is clearly essential if we are to learn how development is controlled and how birth defects might be prevented. It is already providing much new information, with eventual clinical relevance, concerning how genetic information is regulated during embryogenesis, a subject which has previously been a complete mystery. The gulf between those caring for patients with birth defects and those studying development in the laboratory is very deep and wide. It would seem to me extremely foolish to discourage this exciting and valuable new avenue of medical research.

I'm sure you will be hearing from others at Hopkins, as well as from the American Society of Human Genetics, but I wanted to be sure that my "vote" was not left out!

Best wishes,

Sincerely yours,

John W. Littlefield, M.D.
Given Professor of Pediatrics

JWL/ls

University of Illinois
at Urbana-Champaign

Department of Physiology and Biophysics

College of Liberal Arts and Sciences
524 Burrill Hall
407 South Goodwin Avenue
Urbana
Illinois 61801
USA

Telephone
Physiology 217 333-1735
Biophysics 217 333-1630

October 12, 1984

Dr. William J. Gartland, Jr.
Executive Secretary
Recombinant DNA Advisory Committee
Building 31, Room 3B10
National Institute of Health
Bethesda, MD 20205

Dear Dr. Gartland:

I would like to register strong objection to the amendments to the Guidelines proposed by Mr. Jeremy Rifkin (Federal Register, Vol. 49, pages 37016-37017, September 20, 1984). A blanket ban on insertion of genes of one mammaliam species into the germ line genome of a second mammalian species could greatly limit proper and important research on the mechanisms involved in gene expression. The obvious potential applications of this kind of research to understanding cancer and genetic disesases need not be enumerated here. That this kind of research can be construed as cruelty to animals by depriving them of the purity of their species is simply absurd. Years of selective breeding and crossbreeding of domestic animals has long since established the principle of species plasticity. I also suspect that if a specific animal gene could be successfully used to cure a serious human genetic disease, the patients and their families would manage to refrain from condemning the treatment. The proposal by Mr. Rifkin, I believe, has no rational basis and intends to correct an injustice that in fact does not exist. I urge the committee to reject the proposed amendments.

Sincerely,

Byron Kemper

Byron Kemper
Associate Professor of Physiology

BK/pd

cc: W. L. Hurley

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Athens County Board of Mental Retardation
and Developmental Disabilities

801 W. Union Street
Athens, Ohio 45701
614/594-3539

Beacon School

Athens County Sheltered
Workshop [ATCO, Inc.]

October 10, 1984

Director
Office Recombinant DNA Activities
Building 31
Room 3B10
National Institute of Health
Bethesda, Maryland 20205

TO WHOM IT MAY CONCERN:

RE: Proposed Addition of Prohibited Experiments to the Guidelines

It has come to our attention that a representative of the Foundation on Economic Trends, Washington, D.C. submitted a letter to the National Institutes of Health to amend guidelines for recombinant DNA experimentation to prohibit any experimentation involving the transfer of a genetic trait from a human being into the germ line of another mammalian species and to also prohibit any experimentation involving the transfer of a genetic trait from any mammalian species into the germ of a human being.

We do not support this recommendation. Research utilizing this procedure could be very helpful to many populations. One research area presently utilizing this procedure is a search for the cure of metachromatic leukodystrophy which handicaps children at an early age. If this procedure is prohibited, the search for a cure for this genetic problem will be limited and this would be disastrous to many young children.

Our school personnel work with a family who have two young daughters with a diagnosis of metachromatic leukodystrophy. There are many genetic diseases as well as cancer, which could be cured or eliminated through continuing research in recombinant DNA.

It is our hope that you will continue recombinant DNA research so more people will have an opportunity to become healthy, happy, productive individuals.

Sincerely,

William L. Korner
Superintendent

Nanette Borkowski
Assistant Superintendent

Daryl G. Upole III
Business Manager

WLK/NB/DGU/jas

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IBA

Industrial Biotechnology Association
2115 East Jefferson Street
Rockville, Maryland 20852
Telephone: (301) 984-9598

Harvey S. Price
Executive Director

October 12, 1984

Dr. William J. Gartland, Jr.
Executive Secretary
Recombinant DNA Advisory Committee
National Institutes of Health
Building 31, Room 3B10
Bethesda, MD 20205

Dear Dr. Gartland:

The following comments to the National Institutes of Health's Recombinant DNA Advisory Committee (RAC) are submitted on behalf of the Industrial Biotechnology Association (IBA), a trade association representing many of the leading commercial biotechnology companies. A current membership roster is attached.

RAC has been requested to modify the NIH Guidelines for Research Involving Recombinant DNA Molecules such that a specific class of genetic experiments would be prohibited. Such experiments involve the transfer of a genetic trait from one mammalian species into the germ line of another, unrelated mammalian species. This request is made not in response to any demonstrated danger, but rather because these experiments are said to violate species integrity and are therefore morally and ethically objectionable. We oppose the request as unreasonable and illogical. Philosophical arguments of this type have been invoked throughout history to obstruct scientific inquiry, and fail to take into account the benefits that have consistently accrued to society from such free inquiry.

Initially, instead of focusing on philosophical and moral arguments, it is important to consider the implications of the petition's argument. The techniques of molecular biology have permitted scientists to unravel many of the secrets of gene structure and function. Early research concentrating predominantly on the simple bacterium Escherichia coli paved the way for a greater understanding of the more complex higher organisms. Research on the genetics of maize pointed to the instability of genetic material, and demonstrated that genes are not in a fixed position on a chromosome but may be translocated. Over the past several years, such research has formed the foundation for mechanistic studies on carcinogenesis. As one major result of this research, scientists have identified a number of oncogenes and their means of action. The ability of scientists to transfer genetic information between organisms has

undergone a quantum jump in the last 15 years with the refinement of various genetic techniques, including recombinant DNA. Only recently have experiments involving the transfer of genetic information to mammalian germ line cells been conducted. These experiments offer scientists a tool for looking at some of the ways in which genes are regulated and expressed, and also offer embryologists a new method for studying cell development. It would be unwise for such avenues of research to be closed off since they appear poised to present mankind with valuable knowledge and benefits.

Requests such as the one in question have the serious consequence of undermining substantial portions of basic research, since one cannot predict the course of scientific experimentation or the mechanisms by which discoveries might be made. Therefore, significant demonstrated or at least apparent danger should be necessary to justify the drastic restrictions that the petition seeks. The petition, however, offers only vague, unsupported assertions of inappropriateness. On the question of moral considerations, it fails to even note that the recent President's Commission report probing societal issues expressly considered such experimentation and did not oppose it. The issues raised are not novel; they have been previously discussed by RAC and noted by other governmental oversight groups, and are now likely to receive continuing attention. Thus, it is not that moral considerations are being ignored. Rather, there have been no compelling scientific or societal reasons presented so far which would make the petition's request a reasonable one.

The request also calls for the protection of germ line cells in nonmammalian species, yet it is even less clear how such cells are allegedly endangered by genetic technologies. Conventional plant breeding practices involve the modification of genetic material from numerous organisms. New hybrid plants are produced for agricultural purposes each year without damaging the genetic diversity of existing plants. The protection of genetic diversity has been encouraged by the agricultural community so that basic crop plants can continue to be improved. Advances in plant molecular biology offer a new mechanism by which genetic diversity can be used to increase agricultural benefits to society, and should be encouraged.

In sum, the petition seeks to impede socially and commercially valuable research for reasons that are fundamentally unsound, and we feel strongly that it should be rejected. We appreciate the opportunity to express these views, and would be pleased to assist the NIH/RAC with further consideration of the issues raised herein.

Sincerely,

Henry S. Pitcairn

HSP/ag
Enclosure

IBA

MEMBER COMPANIES

INDUSTRIAL BIOTECHNOLOGY ASSOCIATION

ACTAGEN, INC.
Elmsford, New York

AGRIGENETICS CORPORATION
Boulder, Colorado

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JOHNSON & JOHNSON
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LIFE TECHNOLOGIES, INC.
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PHARMACIA INC.
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PHILLIPS PETROLEUM COMPANY
Bartlesville, Oklahoma

PORTON INTERNATIONAL
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United Kingdom

ROHM AND HAAS COMPANY
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SCHERING-PLOUGH CORPORATION
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G. D. SEARLE & COMPANY
Chicago, Illinois

SHELL OIL COMPANY
Houston, Texas

STANDARD OIL COMPANY (Indiana)
Naperville, Illinois

TRANSGENE
Paris
France

THE UPJOHN COMPANY
Kalamazoo, Michigan

UNIVERSITY OF MINNESOTA
TWIN CITIES

Office of the Dean

College of Agriculture
277 Coffey Hall
1420 Eckles Avenue
St. Paul, Minnesota 55108
(612) 373-0921

MEMORANDUM

October 11, 1984

TO: Director, Office of Recombinant DNA Activities
Building 31, Room 3B10
National Institutes of Health
Bethesda, MD 20205

FROM: C. Eugene Allen C. Eugene Allen
Dean, College of Agriculture and
Associate Director of Minnesota Agricultural Experiment Station

RE: Proposal by Mr. Jeremy Rifkin to Prohibit Gene Transfer
From One Species to Another

The above proposal is one that will seriously and unnecessarily restrict the use of genetic engineering techniques to address diseases important to animals and man, and to improve the abiltiy of animals to produce food. This new technology holds promise for improving the welfare of both man and animals. It is unlikely that a gene for a given trait is unique to a species. For example, when genetic resistance to a disease is identified and associated with a gene, this technology holds promise for being able to control the disease in other affected species in addition to other animals of the same species. Some of these diseases are common to man and certain animals. Other examples of genes found in one animal species that would improve food production in other animal species include the gene or genes that control growth rate, milk production and number of offspring per birth. For example, a fecundity gene has been identified in a flock of Merino sheep in Australia which if successfully transferred to cattle could increase the number of twin compared to single births. Such a breakthrough would have a major impact in reducing the cost of producing beef in the U. S. and many countries where feed for cattle is not a limiting factor.

I do not object to appropriate and wise regulations that prohibit experiments that are inappropriate. However, such an important policy decision requires very careful consideration and should not be made without extensive consultation with individuals who are knowledgeable of the potential benefits and deterrents of such regulations. Mr. Rifkin's proposal is too broad and encompassing, and would not be to the ultimate benefit of either humans or animals.

:map

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THE JOHNS HOPKINS HOSPITAL

BALTIMORE, MARYLAND 21205

October 10, 1984

Bernard Talbot, M.D., Ph.D.
Acting Director
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, Maryland 20205

Dear Sir:

I am responding to the proposed prohibition of certain recombinant DNA experiments that has been advanced by Mr. Jeremy Rifkin (Federal Register 49, 37016 (1984)). Mr. Rifkin's stated goal "is to protect the biological integrity of every mammalian species and to prevent a fundamental assault on the principle of species integrity and . . . the right of every species to exist as a separate identifiable creature." These are admirable, but utopian goals that ignore the history of mankind's interactions with domesticated mammalian species.

The selective breeding of animals directed to amplifying or eliminating certain traits has been a human activity since the first mammal was domesticated during prehistoric times. This selection for specific traits (mutated genes) has irreversibly modified the gene pools of innumerable species for man's economic gain and whim. Would Mr. Rifkin condemn and prohibit further selective breeding which is aimed at increasing the productivity and usefulness of domesticated species? Current bioengineering technology stands at the threshold of being able to selectively modify one gene at a time and thereby reduce dependence on selective breeding for altering certain traits. The selection introduction of foreign genes into germ lines is thus a logical extension of animal husbandry and not an attack on "the biological integrity of every animal species."

The all-inclusive prohibition proposed by Mr. Rifkin represents an unwarranted restriction of genetic research. Furthermore, Human Experimentation Committee, which are now functioning at medical research institutions and which follow the current, broad NIH research guidelines, are the appropriate instruments for review of experiments that involve human germ cell modifications.

Sincerely,

Cornelis Van Dop, M.D., Ph.D.

jc

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AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS
—INCORPORATED—

CHARLES YANOFSKY
PRESIDENT

DR. CHARLES YANOFSKY
DEPARTMENT OF BIOLOGICAL SCIENCES
STANFORD UNIVERSITY
STANFORD, CA 94305
TEL.: 415 · 497 · 2413

October 10, 1984

Dr. William J. Gartland
Executive Secretary, RAC
National Institute of Allergy
and Infectious Diseases
National Institutes of Health
Bethesda, Maryland 20205

Dear Dr. Gartland,

As President of the American Society of Biological Chemists, I feel compelled to respond to Jeremy Rifkin's proposed amendment to the NIH Guidelines on Recombinant DNA Research that would prohibit experiments involving transfer of genetic traits from one mammalian species into the germline of another unrelated mammalian species.

I strongly oppose the adoption of this amendment for the following reasons:

The opportunity for viral-mediated transfer of genetic material between mammalian species already exists in nature.

Most genes of different mammalian species are closely related - many are no different than a mutant gene and its normal form. There is no scientific basis for the belief that the individual genes of each species are that unique.

In dealing with certain human diseases, gene transfer may be the only feasible means of overcoming the consequences of a serious genetic defect. We must learn how to perform such transfers so that we may explore how to use this information to plan strategies to aid diseased individuals and their offspring.

Modern medicine already does much to keep individuals with genetic defects alive to the child-bearing age and beyond. Since society and the medical profession welcome these efforts, we must not prohibit exploration of any possibility of correcting a serious genetic defect.

Sincerely yours,

Charles Yanofsky

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cc: Charles Hancock

WESTERN UNION
ROUTE 3B
MOORESTOWN NJ 08057 16AM

Western Union Mailgram

4-024777S290 10/16/84 ICS IPMMTZZ CSP RDVA
6092342900 MGMB TDMT MOORESTOWN NJ 129 10-16 0129P EST

DNA

DIRECTOR OF OFFICE OF RECOMBINANT DNA
ACTIVITIES NATIONAL INSTITUTES OF ~~HEALTH~~
BLDG 31
BETHESDA MD 20801

4-0401925289 10-15-84
3135771450 TDBN DETROIT MI 10-15 0340P EST
DUPLICATE OF TELEPHONED TELEGRAM

I AM WRITING IN BEHALF OF THE BOARD OF DIRECTORS OF THE NATIONAL ASSOCIATION FOR SICKLE CELL DISEASE AND THE THOUSANDS OF BLACK PEOPLE WHO EITHER HAVE SICKLE CELL ANEMIA OR THE POTENTIAL FOR HAVING A CHILD WITH SICKLE CELL ANEMIA. IN OUR JUDGEMENT RECOMBINANT DNA SICKLE CELL PROBLEM. THEREFORE WE URGE YOU TO RESIST ALL EFFORTS TO PLACE THE ASSUMED WELFARE OF ANNUALS ABOVE THAT OF THE UNFORTUNATE MEMBERS OF THE BLACK COMMUNITY WHO ARE FORCED TO ENDURE THE RAVAGES OF THIS DISEASE.

CHARLES F WHITTEN MD
WAYNE STATE U SCHOOL OF MED.
540 E CANFIELD
DETROIT MI 48201

1329 EST

MGMCOMP MGM

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5241 (R 7/82)

TO REPLY BY MAILGRAM MESSAGE, SEE REVERSE SIDE FOR WESTERN UNION'S TOLL - FREE PHONE NUMBERS

BAYLOR
COLLEGE OF
MEDICINE

Texas Medical Center
Houston, Texas 77030

Robert J. Kleberg, Jr.
Center for Human Genetics
(713) 799-4773

October 1, 1984

Dr. William J. Gartland
Executive Secretary, RAC
National Institute of Allergy
and Infectious Diseases
National Institute of Health
Bethesda, MD 20205.

Dear Dr. Gartland:

I wish to comment on the August 21st letter of Mr. Jeremy Rifkin to Dr. Bernard Talbot regarding transgenic animal experimentation.

Dr. R. Brinsten and his collaborators have made major contributions to our understanding of tissue specific gene expression. Their important studies have assisted investigators who have interest in improvement of animal stocks.

This knowledge from this analystic method will be important to our understanding of mammalian gene regulation.

Dr. R. Jaenisch has made a significant advancement toward the study of mammalian development genes via transgenic insertional mutagenesis. These important studies provides an improved means of identifying, and characterizing mammalian development in genes. Undoubtedly development genes of the mouse will have their equivalent genes in man. At a time when study of Birth Defects in man is calling for innovative research directions, we would be short sighted to restrict this research.

Investigators developing gene therapy approaches to human heritable diseases would be tremendously set back by Mr. Rifkin's proposal. We have already learned a great deal about the feasibility of somatic gene therapy for man by the successful transfer of E. coli, hamster, and human genes into intact mice. Undoubtedly the efficiency, safety, and sensibility of human gene therapy will be determined by study in the mouse. If transgenic experiments are prohibited, the effort to development of human gene therapy would be severly and adversely affected.

Mr. Rifkin has proposed to stop Research and Development from transgenic research on emotional grounds. He has not examined the tremendous

potential for new genetic knowledge and improved health care approaches. I urge the RDAC of NIH to reject his guideline proposal of August 21st.

Sincerely,

R. Lillian Tenaglio

for C. Thomas Caskey, M.D.
Head of Medical Genetics

cc: Dr. Frank Ruddle
Yale University

CTC:lt

Dictated by Dr. Caskey but signed in his absence

GEORGETOWN UNIVERSITY LAW CENTER
WASHINGTON, D. C. 20001

October 10, 1984

ALEXANDER MORGAN CAPRON
PROFESSOR OF LAW,
ETHICS AND PUBLIC POLICY

202-624-8327

Dr. William J. Gartland
Executive Secretary, RAC
National Institute of Allergy
and Infectious Diseases
National Institutes of Health
Bethesda, MD 20205

Dear Dr. Gartland:

Dr. Ruth Kirschstein has kindly sent me the proposals made by Mr. Jeremy Rifkin in letters of August 21 & 23, with the suggestion that I might wish to communicate comments on these proposals to you in advance of the October 29th RAC meeting.

My comments will be brief because I trust that you will hear at greater length from those who are better able to describe the shaky biological premises on which Mr. Rifkin's proposals rest, as well as their dire consequences for scientific investigation and clinical progress. I will address myself only to the proposition asserted in the August 23 proposal that the NIH should announce that "experimentation involving the transfer of genetic traits between animal and human germ lines to be morally and ethically unacceptable."

As anyone who has thought about the ethics of biomedical research and practice recognizes, it is true that scientific knowledge and discovery of new forms of medical treatment are not the only values, nor necessarily even the highest goals, in an ethical society. On the other hand, they are high values in our society and attempts to control experimentation that stand in the way of advances in knowledge or discovery of medically useful procedures require substantial justification.

It seems to me that this justification is absent in the case of Mr. Rifkin's proposals for two reasons. First, even assuming that the term "genetic trait" has a well established meaning, the "transfer" of the DNA sequence responsible for such a "trait" from one animal to another (a human) might well involve the "transfer" of a DNA sequence very close (perhaps identical) to one that occurs "naturally" in members of the second animal species, but which is more readily available from, better characterized in, etc., the first animal than from fellow members of the second animal's species. The notion (on which the Rifkin proposals apparently rest) that DNA sequences are "species limited"--so that any transfer from one to another violates species integrity--not only ignores Darwinian theories of evolution (based, as is now known, upon DNA changes) but ignores the fact of total or substantial similarity of the DNA sequences among species, including homo sapiens.

Second, the proposal fails to distinguish between the transfer of <u>any</u> trait and the transfer of a sufficiently significant or unique trait between particular species that might justify a prohibition. Confining myself solely to the transfer of traits to or from human beings, I believe that it is possible to conceive of certain transfers (such as those involving human beings' intellectual capabilities) that are <u>prima facie</u> unacceptable (by which I mean that they are unacceptable on their face and that the burden of showing them to be otherwise should rest with the proponents of making such transfers). So far as I know, however, the conclusion reached by the President's Commission in 1982 (in its report <u>Splicing Life</u>, with which I know that you and the RAC members are thoroughly familiar) still stands: none of the experiments now being contemplated reach this limit. Therefore, even a much more precise and less sweeping proposal than the ones put forward by Mr. Rifkin would not be justified.

I hope that these comments are useful for your deliberations.

Sincerely,

Alexander M. Capron

University of Wisconsin—Madison
Laboratory of Genetics
College of Agricultural and Life Sciences and the Medical School
509 Genetics Building
445 Henry Mall
Madison, Wisconsin 53706 (608) 263-1993

October 8, 1984

Dr. William J. Gartland
Executive Secretary, RAC
National Institute of Allergy and
Infectious Diseases
National Institutes of Health
Bethesda, MD 20205

Dear Dr. Gartland:

I have seen a copy of the two amendments to the NIH guidelines for recombinant DNA experimentation submitted by Jeremy Rifkin in his letters to Dr. Talbot dated August 21 and 23.

Rifkin's record as a self-appointed censor of genetic research is well known. I am puzzled that a person with his record is taken as seriously as he is. I am annoyed that he takes up so much valuable time of the Advisory Committee.

There are, of course, serious issues to be discussed, but Rifkin's blanket opposition to any and all gene transfer between mammalian species, if successful, would stop much of the most promising research in genetics — research that is almost certain to bring fundamental insights, useful practical applications, and great humanitarian benefits.

His suggested statement that "the National Institutes of Health considers any such experimentation involving the transfer of genetic traits between animal and human germ lines to be morally and ethically unacceptable" would seem to imply that alleviation of human suffering is not morally or ethically acceptable. These are certainly not my morals and ethics.

The last paragraph of his August 21 letter also argues for similar restrictions on non-mammalian species. This principle, if accepted, would immediately halt a great deal of Drosophila research. In fact, if "non-mammalian species" includes plants, protozoa, and bacteria, what can he mean? Does he propose to stop all research on recombinant DNA? Would he ban experiments on biological control of insects, as alternatives to chemical insecticides, if these involved the use of recombinant DNA? Does he object to such methods to study the malaria parasite? Would he oppose gene transfer experiments in

schistosomes, even if this promised to control schistosomiasis?

Recombinant DNA research has enormous fundamental, economic, and humanitarian possibilities. It would be a major tragedy for the United States if zealots such as Rifkin are permitted to influence research policy.

I hope his proposed amendments will be quickly disposed of.

Sincerely,

James F. Crow

James F. Crow

xc: Dr. Ruth Kirschstein

SOCIETY FOR THE STUDY OF REPRODUCTION

October 12, 1984

Dr. William Gartland
Executive Secretary
Recombinant DNA Advisory Committee
National Institute of Health
Building 31, Room 3B10
9000 Rockville Pike
Bethesda, Maryland 20205

Dear Dr. Gartland:

I am writing concerning the amendment proposed by Jeremy Rifkin on behalf of the Foundation of Economic Trends, 1346 Connecticut Ave., N.W., Washington, D.C. This amendment would seriously compromise progress toward the solution of many medical, agricultural and other problems.

The use of modern technology, such as germ plasm cryopreservation, embryo transfer, etc. is being utilized to preserve germ plasm of endangered species and the genetic variability and integrity of many "non-endangered" species. The technology is being utilized to accomplish the very goals that Mr. Rifkin implies are important. His letter infers that the present lines of research threaten the existence of animal species. Clearly the logic and application are completely contrary to the assumptions implied in Mr. Rifkin's letter.

The types of experiments mentioned in the amendment must go forward to enable mankind to better understand deficiencies and maladies of animals and people. With the development of understanding will come solutions to some problems that today have no means of prevention or cure.

While species obviously differ, many genes are extremely similar, if not identical. The successful study of human anomalies requires appropriate experiments in animal models or use of humans for experiments, if we are going to reduce the afflictions of mankind. History is full of encyclopedic examples of the prevention and/or cure of scourges of mankind resulting from well-designed tests with animal models, using as few subjects as required to draw valid conclusions.

One could write chapters on the dawn of a bright era of biological control, reducing antibiotics, pesticides and other therapy we now accept to maintain high quality food and generally healthy people. The new molecular genetics is a powerful tool for progress. The objectives of the research are consistent with the high moral and ethical standards that we hold in the U.S.

While I will take personal responsibility for this letter, we have had considerable discussion within the Society for the Study of Reproduction. I am confident that these sentiments reflect the vast majority of our members.

Please consider this letter as speaking on behalf of a large body of scientists concerned about the quality of life. This group strongly opposes this amendment as one which would prevent accomplishing the research necessary to improve medicine, agriculture and the general quality of life, along with increased possibilities for maintaining endangered species.

Sincerely yours,

Robert H. Foote

Dr. Robert H. Foote
President

RHF/hs
First class
cc: Dr. M. Lipsett
Dr. N. Scott

The Genetics Society of America
Business Office
Post Office Box 6018
Rockville, MD 20850
301-762-1424

October 9, 1984

Dr. William J. Gartland
Executive Secretary, RAC
National Institute of Allergy and
Infectious Diseases
National Institutes of Health
Bethesda, Maryland 20205

Dear Dr. Gartland:

It has today come to my attention that Mr. Jeremy Rifkin, in letters to Dr. Bernard Talbot dated August 21 and August 23, has proposed amendments to the NIH Guidelines on Recombinant DNA Research and that these amendments are to be considered at the October 29, 1984, meeting of the Recombinant DNA Advisory Committee. The intent of Mr. Rifkin's amendment is to place a constraint, a proscription, on "experimentation involving the transfer of a genetic trait from one mammalian species in to germ line of another unrelated mammalian species", a line of research that in my opinion is potentially of very great value in the health sciences. Adoption of his amendments would place American workers at great disadvantage in this dynamic line of research and not only delay the reaping of its benefits but lead to ultimate importation of the technology from abroad. I do not accept Mr. Rifkin's assertion that this kind of research is "morally reprehensible" and urge that his proposed amendments to the NIH Guidelines on Recombinant DNA Research not be adopted.

Sincerely yours,

R. W. Allard

R. W. Allard, President
Genetics Society of America

RWA:cm

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THE COLLEGE OF WOOSTER
Department of Biology
Wooster, Ohio 44691

October 15, 1984

Director
Office of Recombinant DNA Activities
Building 31, Room 3 B 10
National Institutes of Health
Bethesda, MD 20205

Dear Director:

I write to oppose the recommendation of Mr. Jeremy Rifkin of the Foundation on Economic Trends, Washington, D.C. in his letter submitted to the Recombinant DNA Advisory Committee dated August 21, 1984 regarding prohibiting the transfer of genetic material from one species of mammal to another.

The proposal is detrimental in that it will greatly impede learning about mechanisms of inheritance and control of genetic expression by the most promising of techniques. Secondly, the proposal comes from a philosophy based on a misconception of what constitutes species and speciation. Experience thus far seems to indicate there is a very small likelihood of Mr. Rifkin's fear of "genes runnin a muck" occurring when transferred to different species.

The moral issue raised by Mr. Rifkin regarding violoation of the integrity of a species being perpetuated by having 'foreign' DNA introduced into it is indicative of Mr. Rifkin's naive understanding of a species. He seems to ignore the shared inheritance of species and the concept of a genetic pool in defining biological morality.

Therefore on both scientific and moral grounds, I urge the Committee to vote no on Mr. Rifkin's proposal.

Sincerely,

Donald L. Wise
Danforth Professor and Chair
Department of Biology

DLW:blm

Tel. 216/263-2379

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Bernard H. Berne, M.D., Ph.D.
903 North Pollard Street, #6
Arlington, Virginia 22203

October 16, 1984

Director
Office of Recombinant DNA Activities
Building 31, Room 3B10
National Institutes of Health
Bethesda, Maryland 20205

Dear Sir:

It is with deep regret that I note your proposed amendments that were published in the Federal Register of September 20, p. 37016, regarding the transfer of genetic traits from one species to another. I understand that these amendments were sponsored by Jeremy Rifkin of the Foundation on Economic Trends. Mr. Rifkin and his organization are a scourge on science. He and it should be completely ignored.

Your proposed amendments are highly unethical. They carry an unacceptable risk/benefit ratio. They only benefit mammals, and risk human life and health. I really don't care about genetic risks to such species as rats (the cause of many human diseases), mice, and shrews (among the most viscious of animals).

Transfer of genes between animal species (cows and sheep, etc), must be encouraged to the greatest extent possible, including adequate funding. Much of the world is undeveloped. People are starving to death out there by the millions. The transfer of genetic traits between species offers the opportunity of establishing a hybrid vigor that is as yet unprecedented. Animals far superior to those in existence can be produced. Food production in the U.S. and in the Third World can be greatly enhanced.

Of course, some abnormal animals may be produced. Some may even undergo some pain. But then, consider that a dachsund is far from the prototype dog. It may not lead a very comfortable existence. Yet animal lovers propagate these poor creatures without a thought to the ethics involved, and with no benefit whatever to humanity. Clearly, there is no rational reason nor precedent for prohibiting genetic experiments between species. Species are not created by God. Species barriers can and should be broken for the benefit of both man and animal.

A Pekinese dog is very small. A Great Dane is very large. It is impossible to interbreed these two. If the intermediate dog forms were to become extinct, the two would become unrelated species. They cannot mate. Yet, you would allow genetic transfers between them. Your regulations are indeed arbitrary and capricious. Stop regulating this kind of thing. It is a classic example of government interference.

Some may worry that new engineered species may displace the natural species, and cause their extinction. This is possible, if unlikely. Domesticated Guernsey cows outnumber their wild ancestors. But this is just part of natural selection. It has both benefits and hazards.

Regarding gene transfers from human to animal. Allow them. We can learn much about the causes and treatment of many human diseases such as diabetes by this type of experiment.

It is possible that some human intelligence genes might be transfered as well, perhaps inadvertently. There is, however, only a negligible chance that an intelligent new form will be produced. You must not prohibit such transfers. It is unethical to allow humans to suffer from genetic diseases, just to avoid the possibility of producing an intelligent mammal of a lower species.

I doubt that anyone could engineer a rabbit to be as intelligent as even a dolphin, let alone a human. There is too much technology involved. Fear of this type of thing is behind your misguided regulation. Like most of the fears in recombinant DNA work, this one is unjustified. You are well aware of your previous excessive regulations that have since been modified because they were unsupported by either scientific evidence or common sense. Don't repeat your mistakes.

You also must not prohibit the transfer of mammalian species genes into humans. I would like to have the wings of a bat, the disease resistance of a sewer rat, and the strength of a horse. I would not object if my descenderts had these things. Again, genetic diseases may be prevented in humans by this type of transfer.

Naturelly, there are risks to introducing animal genes into the human genome. A person might not talk, but might moo like a cow. This is not an excuse to prohibit such experiments entirely, however. With time and learning, they can be controlled. Animal experiments should lead the way. Eventually, we may really be able to improve the human genome to eliminate certain diseases without risk. But only if experimentation is not prohibited by stupid bureaucrats and emotional, and equally stupid, activists. Prohibiting such studies is morally wrong and unethical. Despite your wording in the regulation.

Enough said.

Sincerely yours,

Bernard H. Berne

Bernard H. Berne, M.D.

UNIVERSITY OF WISCONSIN--MADISON

DEPARTMENT OF MEAT
AND ANIMAL SCIENCE

Room 256
Animal Sciences Building
1675 Observatory Drive
Madison, Wisconsin 53706

October 15, 1984

Dr. William J. Gartland
Executive Secretary, RAC
National Institute of Allergy and
Infectious Diseases
National Institutes of Health
Bethesda, MD 20205

Dear Dr. Gartland:

I wish to express opposition to the Rifkin proposals of August 21 and 23 which were intended to prohibit transfer of genes between unrelated mammalian species. I am a professor of reproductive physiology in the Department of Meat and Animal Science. I have taught and published in this area for 24 years. Our research and that of my department is devoted to development of ways to more efficiently produce food for an increasingly starving world and to improvement in the quality of the food we eat. Our research presently concerns the introduction of genes of other species into the germ line of food producing species and the multiplication of the resulting zenogenous embryos. We believe this research will, for example, through the introduction and exogenous regulation of a foreign growth hormone gene provide genetic stocks which require 25 to 30% less food to produce a pound of meat and are capable of at least 15% more milk production. Engineering the genes of rumen microorganisms to digest cellulose and lignin will mean that cows, sheep and water buffalo in world land areas of human starvation can convert branches of trees, brush, weeds and fibrous plant residues to needed human food.

The introduction of exogenous genes from species resistant to diseases is expected to allow the use of food efficient or high producing livestock in areas of the world where they might not normally survive.

Many species of natural importance and of importance to man are near extinction. Gene transfer holds great promise for saving endangered species from extinction by incorporating survival traits from another species into their genome. The genes to be transferred are not artificial or foreign to the animal kingdom or the evolutionally ancestors or relatives of the recipient species. Indeed, the gene transfer process may only speed adaptive genomic changes which could occur naturally over many generations of selection. Research concerning gene transfer in laboratory and food producing species is expected to answer basic questions concerning mechanisms regulating gene expression. Answers to these questions are essential for the development of somatic cell gene therapy programs with potential for curing a large array of diseases in individual patients including diabetes and several forms of cancer.

For all the above reasons the benefits to the human and animal population derived from interspecies transfer of genes are great. Indeed, the slight

diversity created in a species from introduction of an exogenous gene is likely to be beneficial to the survival and well being of that species.

Historically, humans have survived as a species because there existed genetic diversity, because the mind of man has been free to invent and because man has had the intellectual ability to control the application of invention without restriction of the invention itself. Placing restrictions on invention or research leading to invention restricts the ability of humans to adapt to a changing environment or to control food supply to meet the needs of all humans. This leads to class distinctions of those with and without adequate food. Insufficient food leads to social unrest and wars far more devastating to the survival of mankind than the addition of a gene to the genome of a species providing food for man. Indeed, the added gene to the genome of a cow, sheep or pig may add to the diversity of that species in a way which enhances its survival or well being as countless mutations have done through the generations.

I urge the Recombinant DNA Advisory Committee to consider proposals to introduce modified exogenous genes into the germ line of living organisms on the merit of each proposed experiment. The broad sweeping, simplistic authoritarian edict proposed by Rifkin is not supportable by scientific understanding of genetic or population biology. In fact, adoption of the proposed amendments presents a distinct risk to the survival of man and animals in our constantly changing environment.

The Recombinant DNA Advisory Committee should continue to develop guidelines, policy and recommendations based on safety, documented risk and benefit to society. Adoption of regulations of policy broadly restricting research on the transfer of genes across species will likely result in the research and its application occurring in an uncontrolled and undisclosed manner outside the United States and in private industry. In part this has happened already with human in vitro fertilization and has resulted in a poor data base of primate research from which decisions about procedures put into practice in human IVF can be made.

I strongly urge rejection of Rifkin's two proposals.

Sincerely,

Neal L. First

Neal L. First
Professor

cc: R. G. Cassens
N. A. Jorgensen
L. M. Walsh
R. R. Burgess

Rt 1 Box 311
New Marshfield OH
45766

October 10, 1984

Director
Office Recombinant DNA Activities
Building 31
Room 3B10
National Institute of Health
Bethesda, Maryland 20205

To Whom It May Concern:

The public first heard of DNA research a little more than 15 years ago. Now the discoveries about DNA dominate modern medicine and are the foundation and fundamental to the current study of medicine. Are we able to turn away from this?

Mr. Jeremy Rifkin has presented an emotional and moral appeal to halt recombinant DNA research. He states: "that such an intrusion violates the telos of each species and is to be condemned is morally reprehensible." Telos is Greek meaning end, completion, perfection. Are we at the end? Is now the completion or perfection of the human condition?

Organisms continues to evolve. With the development of instruments designed to study DNA has come the discovery that genetic material has the ability to transfer without human intervention or manipulation.

There is, as in other discoveries, a potential for abuse in the application of the science. I applaud the presence of the Recombinant DNA Advisory Committee. It is essential to have research reviewed in the light of the scientific community. Open dialogue is basic to responsible goal setting and implementation. Public access and awareness is followed by understanding and support.

Recombinant DNA research is the hope for understanding and conquering cancer and genetic disease. It must continue if we hope to cure these ills and better our world.

Sincerely,

Phil Henry

Bijan Ahmadi, M. D.
SURGICAL CENTER
SUITE 103
WESTPORT ROAD AND CARDINAL DRIVE
ELIZABETHTOWN, KENTUCKY 42701
(502) 737-4343

PRACTICE LIMITED TO
ORTHOPAEDIC SURGERY

October 5, 1984

Director, Office of Recombinant DNA Activities
Building 31, Room 3BIO
National Institute of Health
Bethesda, MD 20205

Dear Director:

I wish to respond to the proposed amendment to the National Institute of Health's Guidelines for Research involving Recombinant DNA Molecules as submitted by Mr. Jeremy Rifkin of the Foundation on Economic Trends.

My daughter made me aware of Mr. Rifkin's proposal to discontinue research important to the cure of genetic disorders, cancer and other diseases. I am strongly urging the committee to overrule the proposed amendment and continue the funding for Recombinant DNA Activities.

Sincerely,

Dr. Bijan Ahmadi, M.D.

THE JOHNS HOPKINS UNIVERSITY
SCHOOL OF MEDICINE

DEPARTMENT OF
MOLECULAR BIOLOGY AND GENETICS

725 N. WOLFE STREET
BALTIMORE, MARYLAND 21205

October 17, 1984

Dr. William J. Gartland, Jr.
Executive Secretary
Recombinant DNA Advisory Committee
Building 31, Room 3B10
National Institutes of Health
Bethesda, Maryland

Dear Dr. Gartland:

I am writing concerning the proposals for prohibition of experiments involving mammalian interspecies germ line gene transfer, as described in the Federal Register of September 20, 1984. Experiments of this kind are likely to be of increasing importance in studying growth and differentiation, in developing models of human disease, and in animal breeding. Sometimes these experiments will require genes from a species different from the recipient or partially or entirely synthetic genes. Therefore one should have a very good reason to prohibit experiments of this kind. In my opinion, the arguments for prohibition lack merit. I don't see how transfer of one or several genes into the germ line of experimental animals would threaten the "biological integrity" of the species. I urge the Recombinant DNA Advisory Committee to reject both proposals.

Sincerely,

Daniel Nathans

Daniel Nathans

DN/dhw

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STANFORD UNIVERSITY SCHOOL OF MEDICINE
VETERANS ADMINISTRATION MEDICAL CENTER
3801 Miranda Avenue
Palo Alto, California 94304

DEPARTMENT OF MEDICINE

Area Code 415
493-5000
Ext. 5505

October 18, 1984

Director
Office of Recombinant DNA Activities
Building 31, Room 3B10
National Institutes of Health
Bethesda, Maryland 20205

Dear Director:

I am writing to express my concern regarding the proposals by Mr. Jeremy Rifkin to amend the Guidelines regarding recombinant DNA research. Mr. Rifkin's abhorent proposals are an attempt to ban all transfer experiments of genes between one species and the germ line of another. Mr. Rifkin's concern is with the moral and ethical nature of such experiments, not with their potential biological or ecological hazards. I respectfully point out to the RAC that its authority extends only to providing advise as to the potential biological and ecological hazards of recombinant DNAs. Thus, in my opinion, Mr. Rifkin's amendment does not fall within the scope of the RAC's authority. The fact that Mr. Rifkin is an ignoramus, and that his proposed amendments are the work of an unbalanced mind should not influence the committee's judgement that his amendments do not relate to the scope of the Guidelines.

Sincerely yours,

Laurence H. Kedes, M.D.
Professor of Medicine

LHK/sk

DEPARTMENT OF HEALTH & HUMAN SERVICES

National Institutes of Health
National Cancer Institute

Memorandum

Date: October 18, 1984

From: Chief, Laboratory of Molecular Pharmacology, DTP, DCT, NCI

Subject: Proposed Amendments to NIH Guidelines

To: Director, Office of Recombinant DNA Activities
Bldg. 31, Room 3B10

I am responding to the invitation from Public Comment on the proposals to be considered by the NIH Recombinant DNA Advisory Committee to prohibit experiments involving mammalian gene transfer. My laboratory is not now and will not in the foreseable future be engaged in this type of work, so that the proposed actions will in no way affect my laboratory program.

I am strongly opposed to the two amendments sponsored by Jeremy Rifkin of the Foundation on Economic Trends. The proposed amendments would invoke very broad restrictions covering all gene transfers between the germ lines of unrelated mammalian species, including humans. Because of the great variety of experiments that are possible, one cannot foresee the ultimate benefit or detriment. It seems to me that this type of research could lead to extraordinary benefit to mankind. Technological advances generally can be abused, and we do need better monitoring of specific areas to which new technology will be applied. But blanket restrictions such as those proposed would cripple science and its potential for solving human problems.

Kurt W. Kohn, M.D., Ph.D.

Center for Health Sciences
University of Wisconsin-Madison
University Hospital and Clinics

600 Highland Avenue
Madison, Wisconsin 53792

October 19, 1984

Director
Office of Recombinant DNA Activities
Building 31, Room 3B10
National Institute of Health
Bethesda, MD 20205

Dear Director:

I have recently had the opportunity to review the Rifkin Amendments which I believe reflect a rather naive approach to this problem. Such constraints as he proposes would seriously impair both ongoing and future research in this area that could very well have importance in hoped-for ultimate therapy of such genetic disorders as Duchenne muscular dystrophy.

As a member of the Medical Advisory Board of the Muscular Dystrophy Association, I would like to express my objections to this unscientific proposal, which, because of its probable affect on research and hopefully treatment, poses a very amoral act.

Sincerely yours,

Henry A. Peters, M.D.
Professor
DEPARTMENT OF NEUROLOGY

HAP:dj

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Department of Mathematics
Duke University
Durham, NC 27706
17 October 1984

Director, Office of Recombinant DNA Activities
Building 31, Room 3B10
National Institutes of Health
Bethesda, Maryland 20205

Dear Sir:

Friends have informed me of Jeremy Rifkin's proposal to limit certain types of recombinant DNA research. I am told that the proposal could have a debilitating effect on research toward effective treatment of genetic disorders such as metachromatic leukodystrophy, sickle-cell anemia, and diabetes.

While I recognize that there are dangers in recombinant DNA research, I nonetheless feel that low-risk research with high potential pay-off should be encouraged.

My friends have a personal stake in this matter--two daughters who face almost certain death from metachromatic leukodystrophy unless there is a research break-through.

Please act to establish a wise and humane policy for recombinant DNA research.

Sincerely yours,

H. Erick Layton

CARNEGIE INSTITUTION OF WASHINGTON
DEPARTMENT OF EMBRYOLOGY
115 WEST UNIVERSITY PARKWAY
BALTIMORE, MARYLAND 21210
TELEPHONE: 467-1414

October 17, 1984

Director
Office of Recombinant DNA Activities
Building 31, Room 3B10
National Institutes of Health
Bethesda, Maryland 20205

Dear Director:

I wish to comment briefly upon recent proposals made to the RAC by Mr. Jeremy Rifkin to ban the transfer of genetic information between species. I am speaking as a scientist who is very much concerned about human welfare and as a member of the Muscular Dystrophy Association Scientific Advisory Board.

Over the past few years I have seen the development of some real promise for the cure of formerly incurable genetic disorders such as muscular dystrophy and cystic fibrosis. For the first time, it seems likely that these horrible burdens man has always born will soon yield to the advances in molecular genetics. If there were ever an appropriate time to repress scientific investigation, this is surely not it.

Without taking serious risk we are now able to use gene transfer to learn the molecular nature of these terrible genetic disorders. Without taking serious risk we are approaching the point at which it will be practical to consider molecular level intervention to actually cure these diseases and in some cases to rid the world of these diseases. In my opinion it would be morally and ethically wrong to stand by now and not bring these cures into being. As I understand Mr. Rifkin's argument, the reason for his suggestion that gene transfer experiments be disallowed has to do with some ethical and moral concern for purity of species. I see no merit in his point of view on ethical and moral grounds. I do see a sort of parallel between his view and racist views of the past in which racial "purity" was elevated to the level of a moral imperative. We know what that led to. I am solidly for continuing the pursuit of knowledge for the benefit of mankind, and I see recombinant DNA research clearly aimed in this direction. Thus, I wholeheartedly disagree with Mr. Rifkin's position and urge rejection of his suggestions to repress gene transfer experiments.

Sincerely yours,

Douglas M. Fambrough

DMF/sds

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University of Wisconsin-Madison

Office of Biological Safety
1552 University Avenue
Madison, Wisconsin 53706
Tel. (608) 263-2037

October 20, 1984

Dr. William Gartland, Director
Office of Recombinant DNA Activities
Bldg. 31, Rm. 3B10
National Institutes of Health
Bethesda, MD 20205

Dear Dr. Gartland:

We, faculty members of the University of Wisconsin-Madison, want to express our opposition to the Rifkin proposals to prohibit genetic transfer between unrelated animal species.

As members of this University's College of Agriculture and Life Sciences, Schools of Medicine - both human and veterinary, as well as the Institutional Biological Safety Committee, it is our collective opinion that such research, when carefully considered and conducted for valid purposes, poses no undue hazard for the ecology and contradicts no generally accepted moral or philosophical values.

On the contrary, to perform such research is consistent with the ethical basis for any biomedical experimentation - to advance knowledge with the hope that this greater understanding can benefit mankind as well as other animal species in our ecology.

It has long been an accepted ethical premise that experiments not possible in human systems should be performed in animal substitutes. In contemporary genetic research it is vital that interspecies manipulations be made in order to understand the development and expression of a gene function under conditions unacceptable in a human system.

As scientists, we believe that we have a moral responsibility to improve human welfare. Since the beginning of agriculture over 10,000 years ago, man has been actively involved in genetic manipulation of plants and animals. Genetic manipulation has been a natural process from selection of mutants that occur naturally, to induction of mutations, and now introduction of specific traits between species. There is nothing unnatural or immoral about genetic change - it has been going on since life began. We now have technical knowledge to accomplish change much more efficiently. This knowledge has a direct benefit for mankind when applied to problems of inherent genetic defects, developmental deficiencies, and the enhancement of human response to disease. Moreover, utilizing information derived from interspecies genetic transfer raises the potential for decreasing human misery by increasing the world's food supply in the face of rising populations and declining resources. This application of genetic technology will be especially important to Third World nations.

Mr. Rifkin's concern for disappearance of germ lines is unfounded. There are widespread and active programs to preserve fundamental germ lines from all over the world. This is particularly true for crop plants. Germ plasm collections provide the raw materials and genetic diversity that are the fundamental base for selection of specific genetic characteristics. It is already well recognized that basic germ lines must be preserved as this is the basic natural library of genetic information that must be drawn upon in the future, in ways that cannot currently be anticipated.

Insofar as germ line preservation is concerned, genetic transfer holds great promise that some endangered species may be saved from extinction by virtue of incorporating survival traits from one species to another.

We stress that not a single risk scenario has materialized in the past 15 years since the introduction of recombinant DNA technology and its present widespread application. We agree, however, that whatever risks are involved or ethical values challenged should be carefully considered and weighed against the benefits derived by such experimentation. We endorse the practice of subjecting such genetic experimentation of both intra and interspecies nature to the scrutiny and criticism, when merited, of the Recombinant Advisory Committee as well as an institution's Biological Safety Committee and (if appropriate) to its Human Subject and Animal Experimentation Committees as well. But, like R.A.C.'s evaluation of specific genetic experimentation, when regulations are introduced to prohibit or restrict such research they should be subject to the same careful evaluation of risks and benefits before they are enacted.

We believe that the appropriate mechanisms are already in place for the conduct of such research and that it would be superfluous to add new ones. We reject the unsubstantiated notion that interspecies genetic transfer must be prohibited solely for the sake of genetic integrity. In all probability, germ line integrity does not exist in nature because of the widespread gene flow vectored by viruses and other vehicles for natural interspecies transfer.

We urge the R.A.C. to reject the Rifkin proposals.

(signatures on following pages)

Donn J. D'Alessio, MD
Chairman, Institutional Biosafety Committee
Chairman, Dept. of Preventive Medicine

Richard R. Burgess, PhD
Professor, Oncology, McArdle Laboratories
Director, UW Biotechnology Center

James A. Miller, PhD
Professor, Oncology
McArdle Laboratories

Henry C. Pitot, MD, PhD
Professor, Oncology
Director, McArdle Laboratories

Elizabeth C. Miller, PhD
Professor, Oncology
Assoc. Director, McArdle Laboratories

Richard A. Spritz, MD
Asst. Professor, Genetics and Pediatrics

Frederick R. Blattner, PhD
Professor, Genetics

Roland R. Ruechert, PhD
Professor, Biophysics and Biochemistry

Gary A. Splitter, PhD
Assoc. Professor, Veterinary Science

Jack Gorski, PhD
Professor, Biochemistry and Animal Science

Bernard C. Wentworth, PhD
Professor, Poultry Science

Ronald D. Schultz, PhD
Chairman, Pathobiological Sci., Veterinary Med.
Professor, Medical Microbiology

Thomas M. Yuill, PhD
Assoc. Dean, Veterinary Medicine
Professor, Pathobiological Sciences

Waclaw T. Szybalski, D.Sc
Professor, Oncology
McArdle Laboratories

Neal L. First, PhD
Professor, Animal Science

Max J. Rosenbaum, PhD
Biological Safety Officer

THE UNIVERSITY OF CONNECTICUT
HEALTH CENTER

October 16, 1984

Dr. William J. Gartland
Executive Secretary, RAC
Bldg. 31, Room 3310
National Institutes of Health
Bethesda, MD 20205

Dear Dr. Gartland:

I am writing to express my strong opposition to the two proposed amendments to the NIH Guidelines submitted by Jeremy Rifkin concerning gene transfer into germline across mammalian species. His stated rationale for these proposals is without scientific basis and is, indeed, directly contrary to everything we know about genetics and speciation. First, the notion that any species has a fixed genome and that change in any single gene threatens the fundamental integrity of the species is simple nonsense, given our current understanding of the degree of polymorphism and genomic plasticity that is the norm within a well-defined species. The implicit corollary, that a species is defined by the sequence of any (or every) gene, is therefore a logical absurdity: if the cytochrome c's of human and Macaque monkey differ by a single amino acid residue, does a mutation to identity impose a change of species on that individual? Secondly, the idea that a species has a "telos" is contrary to any evidence provided by biology and belongs rather in the realm of mysticism. That mysticism is a poor basis for sound public policy is amply confirmed by history.

I do share the belief that foreign genetic material should not be inserted into the human germline without the fullest consideration of all the potential implications and the broadest public discussion of these. However, there is no reason to undertake such experiments in the near future; an enormous amount of additional information will be necessary before it is known of such an approach is feasible, much less a preferred route to intervention in human genetic disease. In the meantime, current NIH guidelines and regulations concerning human experimentation clearly provide the requisite safeguards, without the necessity of explicit prohibition. This conclusion appears to be entirely consonant with the recent report of the President's Commission for the study of Ethical Problems in Medicine and Biomedical and Biobehavioral Research.

SCHOOL OF MEDICINE
FARMINGTON, CONNECTICUT 06032-9984

In sum, Mr. Rifkin's proposals can only serve to confuse the public as to the scientific basis of public policy and to pervert or abort the kinds of serious and informed public discussion that are necessary to resolution of complex ethical issues and development of wise policy for the long term.

Sincerely yours,

M.J. Osborn
Professor and Head
Department of Microbiology

THE JOHNS HOPKINS UNIVERSITY

BALTIMORE, MARYLAND 21218

DEPARTMENT OF BIOLOGY

October 9, 1984

Director
Office of Recombinant DNA Activities
Building 31, Room 3B10
National Institutes of Health
Bethesda, MD 20205

Dear Sir:

I wish to comment on the ammendments to the NIH guidelines proposed by Mr. Jeremy Rifkin in his letters of August 21 and 23, 1984. In my opinion, adoption of these ammendments would needlessly and drastically curtail significant amounts of research designed to further the understanding of the genetics of mammalian organisms. As with all such experimentation, one must weigh the potential benefits against the potential risks in order to reach a rational position. These are considered separately below.

1. What are the risks? If there are any, they are not apparent to me. I flatly reject the hypothesis that each species has a telos which is violated by the introduction of foreign genetic material, and find this position to be logically untenable by any objective, rational, and informed person. There are any number of examples of the transfer of genetic material from one species to another in nature, which indicate that species barriers are not absolute. Transfer of genetic material from one species to another actually may be a significant mechanism of evolution. The introduction of genes in the laboratory is not qualitatively different from these naturally occurring phenomena.

If Mr. Rifkin's contention that each species has a right to its species integrity is accepted, then the selective breeding done by farmers for thousands of years would have to be eliminated. It is common practice to selectively breed those animals which express desired characteristics, e.g. high milk production, large size, gentle temperment, etc. Over the years, this breeding leads to considerable alterations in the species involved.

Witness the differences between dogs and jackals, pigs and wild boars, cows and wild cattle, etc. Would Mr. Rifkin stop all selective breeding experiments? Introduction of foreign genetic material represents a quantitative but not qualitative change from the selective breeding experiments. Animals with desired characteristics may be made more quickly and economically than by conventional breeding, but ultimately the same ends would be reached.

2. What are the benefits? In practical terms, it may be possible to generate larger and more efficient animals that will increase the supply and decrease the price of meat and dairy products. If, for example, larger pigs can be generated, then fewer would have to be raised to provide the same amount of meat, which may result in increased economy and certainly will result in a fewer number of pigs which will have to be raised and sacrificed. Thus, in addition to increases in efficiency, these experiments probably will reduce animal suffering.

Other commercial benefits would be the large scale production of medically important products in animals. For example, if large animals could be made to produce large amounts of insulin or interferon, the resulting product would be appropriately glycosylated and otherwise modified and probably would be considerably more effective than the corresponding product made in bacteria. These characteristics would make the product cheaper and more effective, and therefore available to a greater number of people, with a decreased risk of side effects.

To my mind, the commercial benefits pale beside the benefits to be gained from the increased understanding of gene regulation and function which has and will continue to be generated by this technology. Many human diseases result at least in part from alterations in gene structure or function. Recent evidence demonstrates unequivocally that many types of cancer result from a limited number of genetic changes, and heart disease as well has a genetic component. Currently, the best system available to characterize tissue-specific gene regulation and the effects of genetic changes on the phenotype of animals is to return genes into mammalian species, in particular the laboratory mouse. Legislation against this technology would eliminate one of the major routes by which we are slowly gaining an understanding of gene expression in mammalian organisms and would needlessly retard our understanding and ultimately control of many human diseases.

In summation, the potential benefits from this technology are so great both in basic science and in

medically and commercially applied areas of research, while the risks are so minimal, that to abolish the technology would be a shame and a disservice to the American people. In very direct terms, one must consider whether the more rapid alleviation of human diseases and the potential production of medically and commercially important animals justifies the introduction of genes into a few laboratory and domestic animal species (with the purported violation of their telos). In my mind, there is no question.

Sincerely,

George Scangos
Assistant Professor

University of Wisconsin—Madison

LABORATORY OF GENETICS
406 Genetics Building
Madison, Wisconsin 53706

O. Smithies
Office: (608) 262-2976
Laboratory: (608) 262-1047

October 17, 1984

Dr. William J. Gartland
Executive Secretary, RAC
National Institute of Allergy
and Infectious Diseases
National Institutes of Health
Bethesda, MD 20205

Dear Dr. Gartland:

This letter is to comment on the two amendments to the NIH Guidelines for Recombinant DNA Experimentation submitted by Mr. Jeremy Rifkin for possible consideration by the Recombinant DNA Advisory Committee (RAC) at its next meeting on October 29th, 1984.

Mr. Rifkin states that his amendments are to protect "the principle of species integrity" transgression of which "violates the right of every species to exist as a separate, identifiable creature." He also wishes the committee to endorse his view that any transfer of genes between non-breeding mammalian species, particularly when a human is the donor or recipient, is abhorrent and "morally and ethically unacceptable." The basis for Mr. Rifkin's assumed principle of species integrity is not stated by him, nor are any arguments presented to support his personal view that inter-species transfer of genes is morally unacceptable.

I am a Hilldale Professor of Genetics and Medical Genetics at the University of Wisconsin-Madison, a member of the Genetics Section of the National Academy of Sciences, and a past President of the Genetics Society of America. I have been for many years and continue still to be an active investigator in the field of molecular genetics. I use recombinant DNA technology every day in my laboratory. I am also active in studying the natural evolution of genes in various species, including man. In all my studies I am constantly made aware of the great commonality of genetic material. Mammalian species that have no possible means of breeding at the present time have features in their genomes of remarkable similarity. Nowhere do I find evidence supporting any inviolate principle of species integrity. Indeed, there is increasing evidence that genetic material can be transferred from one species to another by viral and other microbial

agents. Such transfers, although infrequent, appear to be natural steps in evolution. Mr. Rifkin is surely not well-informed when he tries to protect a non-existent principle of species integrity.

The moral or ethical basis for forbiding any gene transfer between humans and mammalian species is also unsupported in Mr. Rifkin's statement. He fails to consider the need to investigate the function of normal and defective human genes in animals in order to understand the effects and possible correction of their malfunction in human patients. Nor does he consider other benefits that might be obtained by introducing the genes from one mammalian species into another. One such benefit that can be envisaged is the improvement of our livestock. By all means such experiments should be considered carefully and their potential benefits weighed against any harm they might do. We should also be careful to avoid unwarranted suffering in experimental animals. But Mr. Rifkin is asking for a blanket prohibition on moral grounds. In doing this he shows that his view of morality is sorely limited, for he does not consider the moral harm of allowing human genetic abnormalities, some of which cause great misery, to go uninvestigated when we have available tools for their study and possible treatment. The door would be closed on important avenues to the alleviation of human suffering if Mr. Rifkin's amendments were to be passed.

I urge the Recombinant DNA Advisory Committee to reject both Mr. Rifkin's amendments, on the basis of the unsupported nature of their premises, and because their adoption would prevent the carrying out of many invaluable experiments aimed at avoiding in the future unnecessary suffering in human families in which genetic abnormalities presently occur.

Sincerely,

Oliver Smithies

Oliver Smithies,M.A.,D.Phil(Oxon)
Hilldale Professor of Genetics
and Medical Genetics

OS:FM

University of Illinois
at Urbana-Champaign

Department of Dairy Science
315 Animal Sciences Laboratory
1207 West Gregory Drive
Urbana
Illinois 61801

College of Agriculture
217 333-3462

October 22, 1984

Director, Office of Recombinant DNA
Activities
Building 31, Room 3B10
National Institutes of Health
Bethesda, Maryland 20205

Dear Sir:

We are deeply concerned about the recent proposals made to your committee by Mr. Jeremy Rifkin (Federal Register 49: 37016-37017, 1984) on the transfer of mammalian genes. The proposal is not founded on scientific facts or reasoning and would have far reaching implications in the areas of future world food production and in human health.

Mr. Rifkin's proposal is based solely on ethical issues, reflecting primarily his personal beliefs. No concern is expressed for environmental or safety issues. The "dramatic new technological threshold" expressed by Mr. Rifkin is anything but new. Transfer of DNA to mammalian cells or embryos is a well established technique and research to date has done much to clarify the biological limitations of the approach. An important biological lesson underlined by the use of recombinant DNA techniques is that the genome of organisms is not static, with a number of types of movable elements existing and this dynamic nature of the genome is a mechanism of adaptation to changing environment. Evidence from research in developmental biology strongly indicates that incompatibility within a genome most likely will lead to embryonic death.

Man's efforts to genetically manipulate other species began well before recorded history. Attempts at DNA transfer to confer a special characteristic on population within a species is but a more refined extension of selective breeding used by man for centuries in many species. The successful transfer of DNA in humans to cure genetic disease could scarcely be condemned on ethical grounds. Numerous gene products from other species are routinely used in treating human diseases. The transfer of a gene rather than administration of its product is not a violation of species identity, but simply a more efficient and probably more effective treatment.

Prohibition of gene transfer in animals would severely limit future progress in critical human and animal needs areas and would dramatically cut short the current revolution in biological research. We vehemently oppose Mr. Rifkin's proposed amendments and urge the committee to reject those amendments.

Sincerely,

Charles N Graves, Assoc. Prof., Dairy Science

Mary A Lewis, Asst. Prof., Animal Science

Roger P Shanks, Assoc. Prof., Dairy Science

Walter K Hurley, Asst. Prof., Dairy Science

James L. Robinson, Assoc. Prof., Dairy Science

J. R. Lodge, Prof., Dairy Science

N R Ziegler, Prof., Dairy Science

Keith W Kelley, Prof., Animal Science

THE UNIVERSITY OF TEXAS MEDICAL BRANCH
GALVESTON, TEXAS 77550

DEPARTMENT OF HUMAN BIOLOGICAL CHEMISTRY & GENETICS
Division of Cell Biology

Area Code 409
761-2761

October 19, 1984

Director
Office of Recombinant Activities
Building 31, Room 3B10
National Institutes of Health
Bethesda, MD 20205

Sirs:

I am writing in strong objection to Mr. Jeremy Rifkin's proposal to ban incorporation of genetic materials into the germline across species lines in mammals. In the first place, Mr. Rifkin offers no evidence that such experiments involve any risk to the public--and it is on the basis of risk assessment that the RAC is charged with making its decisions. Instead, Mr. Rifkin offers a set of labored philosophical statements about the inherent rights of species to a separate identity--a subject more suited to the classroom than to a regulatory agency.

If adopted, however, Mr. Rifkin's proposal would have a most far-reaching adverse impact on a promising future approach to treatment of human genetic diseases. Some of those diseases caused by enzyme deficiencies in a well-defined target area may soon prove amenable to treatment by somatic gene therapy, in which the wild type gene would be introduced into somatic cells of the affected organs. However, those diseases whose defect involves a more widespread or unknown target could not be treated in this way, but might be ameliorated by introduction of the wild type gene into eggs before <u>in vitro</u> fertilization. Obviously, detailed animal experiments would have to precede any possible human trials of such a scheme. Since animal models of only a few genetic diseases are avilable, most such experiments would attempt to detect expression of exogenous genes against a wild type background. To establish definitively the nature of any increased expression, heterologous genes would have to be used. But it is precisely those experiments which Mr. Rifkin now seeks to ban. Thus, his proposal would forever seal off this promising area of future research.

This is, I suspect, precisely what Mr. Rifkin really wants to do. His real objective is to prevent manipulation of the human genome with human genes, an idea which has already generated much controversy, partly at his instigation. For fear that his battle there will be lost, he now seeks to make that argument moot by preventing perfection of the necessary techniques. I strongly urge that the RAC reject this ill-advised and unfounded prohibition.

Sincerely,

David A. Konkel

David A. Konkel, Ph.D.
Assistant Professor

DAK:lrj

JANE Z. WOODROW, PH.D.
CLINICAL PSYCHOLOGIST
2 W. STIMSON, SUITE 2
P.O. BOX 277, ATHENS, OHIO 45701

BY APPOINTMENT ONLY

PHONE 614/593-4801

October 11, 1984

Director, Office of Recombinant DNA Activities
Building 31, Room 3B10
National Institutes of Health
Bethesda, Maryland 20205

Dear Director:

I am writing in response to Mr. Jeremy Rifkin's proposed amendment to the National Institute of Health's Guidelines for Research involving Recombinant DNA Molecules as outlined in the September 20, 1984 Federal Register.

I am very concerned that Mr. Rifkin's proposal does not take into consideration the discontinuance of important medical research relative to genetic disorders, cancer, and other diseases. I am specifically interested in the continuation of this research as it relates to a rare genetic disease known as Metachromatic Leukodystrophy. I am familiar with the Downard family in Athens, Ohio who have two young children with this particular disease. It is my understanding that this research is currently the most viable possibility for cure or treatment for these two and many other children suffering from genetic diseases.

I strongly urge the committee not to adopt the proposed amendment and instead continue the funding for Recombinant DNA Activities Research.

Sincerely,

Jane Z. Woodrow

Jane Z. Woodrow, Ph.D.
Clinical Psychologist

167 Morris Avenue
Athens, OH 45701
October 12, 1984

Director
Office of Recombinant DNA Activities
Building 31, Room 3B10
National Institutes of Health
Bethesda, MD 20205

Dear Director:

The September 20, 1984 Federal Register outlined Mr. Jeremy Rifkin's proposed amendment to the National Institute of Health's Guidelines for Research involving Recombinant DNA Molecules.

Mr. Rifkin's proposal would, if adopted, discontinue any further genetic transfer experimentation with laboratory animals and would prohibit much needed research on cancer, genetic disorders, muscular distrophy, diabetes, sickle cell anemia, asthma, and other diseases.

Two young children, very close to me, are suffering from Metachromatic Leukodystrophy--a rare genetic disease that is a terminal illness. It is my understanding that recombinant genetic research is currently the most viable possibility for cure or treatment for these two children and the thousands of other children and adults suffering from genetic diseases.

I am saddened to think that all medical research relative to this disease would be delayed or prohibited. I strongly urge the committee not to adopt the proposed amendment and instead continue the funding for Recombinant DNA Activities Research.

Sincerely,

Bonnie C. Vail
Bonnie C. Vail

October 15, 1984

Director, Office of Recombinant DNA Activities
Building 31, Room 3B10
National Institute of Health
Bethesda, MD 20205

Dear Director:

I am writing in regard to the proposed amendment to the National Institute of Health's Guidelines for Research involving Recombinant DNA Molecules as submitted by Mr. Jeremy Rifkin of the Foundation on Economic Trends.

I am very concerned that Mr. Rifkin's proposal will discontinue research important to the cure of genetic disorders, cancer and other diseases. I am strongly urging the committee to overrule the proposed amendment and continue the funding for Recombinant DNA Activities Research.

Sincerely,

Peggy Hoffman, ACSW
12 Mayapple St. Rt 11.
Elizabethtown, Ky.
42701

October 15, 1984

Director, Office of Recombinant DNA Activities
Building 31, Room 3B10
National Institute of Health
Bethesda, MD 20205

Dear Director:

I am writing in regard to the proposed amendment to the National Institute of Health's Guidelines for Research involving Recombinant DNA Molecules as submitted by Mr. Jeremy Rifkin of the Foundation on Economic Trends.

I am very concerned that Mr. Rifkin's proposal will discontinue research important to the cure of genetic disorders, cancer and other diseases. I am strongly urging the committee to overrule the proposed amendment and continue the funding for Recombinant DNA Activities Research.

Sincerely,

Joan Shipp

Joan Shipp
Hodgenville, KY 42748

256

101 Melissa Street
Elizabethtown, KY 42701
October 15, 1984

Director, Office of Recombinant DNA Activities
Building 31, Room 3B10
National Institute of Health
Bethesda, MD 20205

Dear Director:

I am writing in regard to the proposed amendment to the National Institute of Health's Guidelines for Research involving Recombinant DNA Molecules as submitted by Mr. Jeremy Rifkin of the Foundation on Economic Trends.

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Sincerely,

October 15, 1984

Director, Office of Recombinant DNA Activities
Building 31, Room 3B10
National Institute of Health
Bethesda, MD 20205

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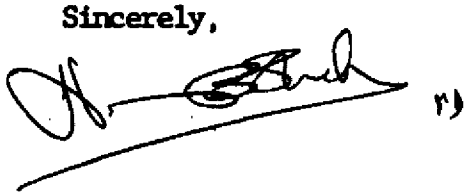
I am very concerned that Mr. Rifkin's proposal will discontinue research important to the cure of genetic disorders, cancer and other diseases. I am strongly urging the committee to overrule the proposed amendment and continue the funding for Recombinant DNA Activities Research.

Sincerely,



N.R. SHAH MD
STAFF PSYCHIATRIST
NORTH CENTRAL COMPREHENSIVE
CARE CENTER,
907 N. DIXIE
ELIZABETHTOWN KY. 42701

258

Revah D. Beach
5834 Madison Twnshp. Rd.
Mt. Perry, OH 43760

Revah Beach
5834 Madison Twp Rd 95
Mount Perry, Ohio
43760

October 15, 1984

Director, Office of Recombinant DNA activities
Building 31, Room 3B10
National Institutes of Health
Bethesda MD 20205

Dear Director:

I am writing in response to the proposed admendment to the National Institute of Health's Guidelins for Research involving Recombinant DNA Molecules as submitted by Mr. Jeremy Rifkin of the Foundation on Economic Trends.

I have a friend with two children with a rare blood disease of which at this time there is no cure. I am a great animal lover but given the choice between my children's or someone else's Children's life, I must put them first.

I am very concerned that Mr. Rifkin's proposed will discontinue research important to the cure genetic disorders, cancer and other diseases. I am strongly urging the committee to overrule the proposed amendment and continue the funding for Recombinant DNA Activities Research.

Sincerely,
Revah Beach

October 5, 1984

Director, Office of Recombinant DNA Activities
Building 31, Room 3B10
National Institutes of Health
Bethesda, MD 20205

Dear Director:

I am writing in response to the proposed amendment to the National Institute of Health's Guidelines for Research involving Recombinant DNA Molecules as submitted by Mr. Jeremy Rifkin of the Foundation on Economic Trends.

I am very concerned that Mr. Rifkin's proposal will discontinue research important to the cure of genetic disorders, cancer and other diseases. I am strongly urging the committee to overrule the proposed amendment and continue the funding for Recombinent DNA Activities Research.

Sincerely,

Barbara A Gibbs

Barbara A. Gibbs
313 East Highland Drive
Zanesville, Ohio 43701

October 15, 1984

Director, Office of Recombinant DNA Activities
Building 31, Room 3B10
National Institutes of Health
Bethesda, MD 20205

Dear Director:

I am writing in response to Mr. Jeremy Rifkin's proposed amendment to the National Institute of Health's Guidelines for Research involving Recombinant DNA Molecules as outlined in the September 20, 1984 Federal Register.

I am very concerned that Mr. Rifkin's proposal does not take into consideration the discontinuance of important medical research relative to genetic disorders, cancer and other diseases. I am specifically interested in the continuation of this research as it relates to a rare genetic disease known as Metachromatic Leukodystrophy. I am familiar with the Downard family in Athens, Ohio who have two young children with this particular disease. It is my understanding that this research is currently the most viable possibility for cure or treatment for these two and many other children suffering from genetic diseases.

I strongly urge the committee not to adopt the proposed amendment and instead continue the funding for Recombinant DNA Activities Research.

Sincerely,

Dorothy Schluessler

Dorothy Schluessler
1830 Aspen Drive
Zanesville, Ohio 43701

261

October 15, 1984

Director, Office of Recombinant DNA Activities
Building 31, Room 3B10
National Institutes of Health
Bethesda, MD 20205

Dear Director:

I am writing in response to Mr. Jeremy Rifkin's proposed amendment to the National Institute of Health's Guidelines for Research involving Recombinant DNA Molecules as outlined in the September 20, 1984 Federal Register.

I am very concerned that Mr. Rifkin's proposal does not take into consideration the discontinuance of important medical research relative to genetic disorders, cancer and other diseases. I am specifically interested in the continuation of this research as it relates to a rare genetic disease known as Metachromatic Leukodystrophy. I am familiar with the Downard family in Athens, Ohio who have two young children with this particular disease. It is my understanding that this research is currently the most viable possibility for cure or treatment for these two and many other children suffering from genetic diseases.

I strongly urge the committee not to adopt the proposed amendment and instead continue the funding for Recombinant DNA Activities Research.

Sincerely,

James E. Bee

James E. Bee
1114 So. Slope Bay
Zanesville, Ohio 43701

October 15, 1984

Director, Office of Recombinant DNA Activities
Building 31, Room 3B10
National Institutes of Health
Bethesda, MD 20205

Dear Director:

I am writing in response to Mr. Jeremy Rifkin's proposed amendment to the National Institute of Health's Guidelines for Research involving Recombinant DNA Molecules as outlined in the September 20, 1984 Federal Register.

I am very concerned that Mr. Rifkin's proposal does not take into consideration the discontinuance of important medical research relative to genetic disorders, cancer and other diseases. I am specifically interested in the continuation of this research as it relates to a rare genetic disease known as Metachromatic Leukodystrophy. I am familiar with the Downard family in Athens, Ohio who have two young children with this particular disease. It is my understanding that this research is currently the most viable possibility for cure or treatment for these two and many other children suffering from genetic diseases.

I strongly urge the committee not to adopt the proposed amendment and instead continue the funding for Recombinant DNA Activities Research.

Sincerely,

Michael F. Whiteman

Michael F. Whiteman
324 Mel Kay Way
Zanesville, Ohio 43701

October 15, 1984

Director, Office of Recombinant DNA Activities
Building 31, Room 3B10
National Institute of Health
Bethesda, MD 20205

Dear Director:

I am writing in regard to the proposed amendment to the National Institute of Health's Guidelines for Research involving Recombinant DNA Molecules as submitted by Mr. Jeremy Rifkin of the Foundation on Economic Trends.

I am very concerned that Mr. Rifkin's proposal will discontinue research important to the cure of genetic disorders, cancer and other diseases. I am strongly urging the committee to overrule the proposed amendment and continue the funding for Recombinant DNA Activities Research.

Sincerely,

Pam Happel
Rt. 1 Box 251
Rineyville, KY 40162
(502) 737-5520

October 5, 1984

Director, Office of Recombinant DNA Activities
Building 31, Room 3B10
National Institutes of Health
Bethesda, MD 20205

Dear Director:

I am writing in response to the proposed amendment to the National Institute of Health's Guidelines for Research involving Recombinant DNA Molecules as submitted by Mr. Jeremy Rifkin of the Foundation on Economic Trends.

I am very concerned that Mr. Rifkin's proposal will discontinue research important to the cure of genetic disorders, cancer and other diseases. I am strongly urging the committee to overrule the proposed amendment and continue the funding for Recombinent DNA Activities Research.

Sincerely,

Doris J. Rockwell
(Mrs. J. H.)

360 Western Circle
Radcliff, KY 40160

Mr. and Mrs. Robert A. Shearer
304 Danville St.
Lancaster, Kentucky 40444

Director, Office of Recombinant
DNA Activities
Building 31 Room 3 B10
National Institutes of Health
Bethesda, Md. 20205

Dear Director:

I am writing in response to the proposed amendment to the National Institutes of Health guidelines for research involving Recombinant DNA molecules as submitted by Mr Jeremy Rifkin of Foundation on Economic Trends.

I am very concerned that Mr Rifkin proposal will discontinue research important to the cure of Genetic disorders, cancer and other diseases. I am strongly urging the committe to overrule the proposed amendment and continue the funding of Recombinant DNA Activities research.

Sincerely,
Mr + Mrs Robert A. Shearer

David L. Lovett
2 Trent Place
The Plains, Ohio 45780

October 12, 1984

Director, Office of Recombinant DNA Activities
Building 31, Room 3B10
National Institutes of Health
Bethesda, MD 20205

Dear Director:

I am writing in response to Mr. Jeremy Rifkin's proposed amendment to the National Institute of Health's Guidelines for Research involving Recombinant DNA Molecules as outlined in the September 20, 1984 Federal Register.

I am very concerned that Mr. Rifkin's proposal does not take into consideration the discontinuance of important medical research relative to genetic disorders, cancer and other diseases. I am specifically interested in the continuation of this research as it relates to a rare genetic disease known as Metachromatic Leukodystrophy. I am familiar with the Downard family in Athens, Ohio who have two young children with this particular disease. It is my understanding that this research is currently the most viable possibility for cure or treatment for these two and many other children suffering from genetic diseases.

I strongly urge the committee not to adopt the proposed amendment and instead continue the funding for Recombinant DNA Activities Research.

Very truly yours,

David L. Lovett

Janet L. Lovett

Director
Office Recombinant DNA Activities
Building 31
Room 3B10
National Institutes of Health
Bethesda, Maryland 20205

To Whom It May Concern:

RE: Proposed Addition of Prohibited Experiments to the Guidelines

I work in a school in which a girl of 28 months is enrolled. This child has a diagnosis of Metachromatic Leukodystrophy. The cause of this disease is a recessive genetic trait which limits the production of Arylsyphatase A. Arylsuphatase A is a chemical which is necessary for proper function of the nerve cell.

This child appeared normal at birth with normal development until age 20 months, she then began regressing and is now unable to walk, talk or even hold her head up. She has a 4 month old sister who has also been diagnosed with the same disease. If the two girls could have gene transfers in the near future, the older girl's progressive disease could be stopped, and the infant could develop normally. If genetic research loses the funding necessary to continue, then the progressive fatal disease of these two children will continue.

There are many genetic diseases as well as cancer, which could benefit from the continuing research in Recombinant DNA.

Please continue Recombinant DNA research so more people in the future may become healthy, happy, productive individuals.

Sincerely,

Craig Brown

New Marshfield, OH 45766

268

October 2, 1984

To Whom It May Concern:

It has come to my attention that Mr. Jeremy Rifkin of the Foundation on Economic Trends, Washington, D.C. submitted a letter to the National Institutes of Health to amend guidelines for recombinant DNA experimentation to prohibit any experimentation involving the transfer of a genetic trait from a human being into the germ line of another mammalian species and to also prohibit any experimentation involving the transfer of a genetic trait from any mammalian species into the germ of a human being.

I DO NOT support this recommendation - Research utilizing this procedure could be very helpful to many populations. One research area presently utilizing this procedure is a search for the cure of metachromatic leukodystrophy which handicaps children at an early age.

If this procedure is prohibited, you are limiting the search for a cure for this genetic problem. This stoppage would be disastrous to many young children.

To reiterate - I DO NOT support the recommendation of Mr. Jeremy Rifkin and I would like to see the guidelines as they are to remain intact.

Sincerely,

Yvonne Fay

New Marshfield, OH 45766

269

October 2, 1984

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Sincerely,

Craig Ahmann

New Marshfield, OH 45766

270

Director
Office Recombinant DNA Activities
Building 31
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Sincerely,

Joan Nadau

New Marshfield, OH 45766

271

Director
Office Recombinant DNA Activities
Building 31
Room 3B10
National Institutes of Health
Bethesda, Maryland 20205

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Sincerely,

Robt M. Romeiser

New Marshfield, OH 45766

272

Director
Office Recombinant DNA Activities
Building 31
Room 3B10
National Institutes of Health
Bethesda, Maryland 20205

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Please continue Recombinant DNA research so more people in the future may become healthy, happy, productive individuals.

Sincerely,

Garland R Reynolds

New Marshfield, OH 45766

273

Director
Office Recombinant DNA Activities
Building 31
Room 3B10
National Institutes of Health
Bethesda, Maryland 20205

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Sincerely,

Barbara Walence

New Marshfield, OH 45766

274

Director
Office Recombinant DNA Activities
Building 31
Room 3B10
National Institutes of Health
Bethesda, Maryland 20205

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Please continue Recombinant DNA research so more people in the future may become healthy, happy, productive individuals.

Sincerely,

Yvonne Ley

New Marshfield, OH 45766

275

October 2, 1984

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To reiterate - I DO NOT support the recommendation of Mr. Jeremy Rifkin and I would like to see the guidelines as they are to remain intact.

Sincerely,

Jean Meade

New Marshfield, OH 45766

276

October 2, 1984

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To reiterate - I DO NOT support the recommendation of Mr. Jeremy Rifkin and I would like to see the guidelines as they are to remain intact.

Sincerely,

Rob + M Rosmeisen

New Marshfield, OH 45766

277

October 2, 1984

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Sincerely,

Garland R Reynolds

New Marshfield, OH 45766

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To reiterate - I DO NOT support the recommendation of Mr. Jeremy Rifkin and I would like to see the guidelines as they are to remain intact.

Sincerely,

Barbara Valence

New Marshfield, OH 45766

279

October 5, 1984

Director, Office of Recombinant DNA Activities
Building 31, Room 3B10
National Institute of Health
Bethesda, MD 20205

Dear Director:

I am writing in response to the proposed amendment to the National Institute of Health's Guidelines for Research involving Recombinant DNA Molecules as submitted by Mr. Jeremy Rifkin of the Foundation on Economic Trends.

I am very concerned that Mr. Rifkin's proposal will discontinue research important to the cure of genetic disorders, cancer and other diseases. I am strongly urging the committee to overrule the proposed amendment and continue the funding for Recombinent DNA Activities Research.

Sincerely,

James Haire

Office of the Principal
Elizabethtown High School
620 N. Mulberry St.
Elizabethtown, KY 42701

280